IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:
NICKOLSON, Victor

Serial No.: 10/089,542 Group: 1614

Filed: March 29, 2002 Examiner: B. Y. S. Kwon

For: DRUG COMBINATION FOR THE TREATMENT OF HEADACHE COMPRISING A NON-STEROIDAL ANTI-INFLAMMATORY DRUG

PETITION UNDER 37 C.F.R. §1.181:
PETITION TO WITHDRAW IMPROPER ABANDONMENT

Honorable Commissioner of Patents
Alexandria, VA 22313

April 12, 2004

Dear Sir:

In response to the Notice of Abandonment and Interview Summary mailed April 7, 2004, Applicants respectfully petition that the Notice of Abandonment is improper and should be withdrawn. Applicants respectfully request withdrawal of the Notice of Abandonment and entry of the Response of September 16, 2003 and Information Disclosure Statement of September 16, 2003.

Response to June 18, 2003 Office Action

Applicants responded timely to the Office Action mailed June 16, 2003. Applicants mailed an Amendment under 37 C.F.R. §1.111 and an Information Disclosure Statement on September 16, 2003. Applicants have attached these documents to this communication. In addition, Applicants have attached the Certificate of Mailing

Under 37 C.F.R. §1.8 signed by Katrina Mears, Intervet Patent Department Administrator.

Applicants respectfully submit that a Response was filed timely.

Interview Summary Analysis

Applicants respectfully address the contents of the Interview Summary. On March 10, 2004, Examiner Kwon contacted Applicants' representative and inquired about a response to the June 18, 2003 Office Action. Applicants can document the date of March 10, 2004 because Applicants' representative responded to the inquiry by resending the Applicants' response to the June 18, 2004 Office Action.

Attached to this communication is the Response to Examiner Telephone Communication that was sent March 10, 2004 to the USPTO by facsimile. Applicants include the facsimile history report that shows that at 5:09 pm March 10, 2004 a facsimile was sent.

Therefore, the Interview Summary is incorrect that March 14, 2004 was a date of communication. Applicants would also note that on April 1, 2004, the second day of communication, Applicants' representative was attending the ABA-IPL CLE course in Washington D.C. and did not receive the voice mail message until his return to the Office in Millsboro, DE on April 5, 2004. Applicants' representative contacted Examiner Kwon early April

5, 2004 to report that a second response was filed March 10, 2004, but the Examiner reported that the instant Notice of Abandonment had already been mailed.

Therefore, Applicants did respond to both inquiries by the Examiner. Applicants believe they have been diligent in pursuing this application and that the Notice of Abandonment does not reflect any inaction taken by Applicants.

Applicants respectfully request that the abandonment be withdrawn and the Information Disclosure Statement and Response filed September 16, 2003 be considered, because, in fact, they were timely filed.

Patent Term Extension

Applicants respectfully request that any lost patent term due to this improper abandonment be added at the issuance of the patent grant. Applicants believe the time lost should be calculated from the September 16, 2003 day of our timely response to the time this petition is granted and the application is examined by the Examiner.

Conclusion

Applicants filed the response timely and respectfully request the Examiner to consider the attached 37 C.F.R. §1.111 Amendment

and Information Disclosure Statement.

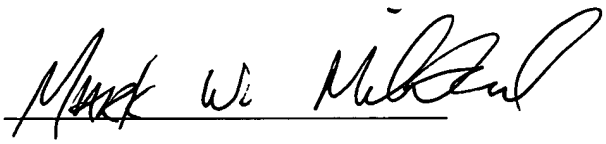
If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (302) 934-4395, in Millsboro, Delaware.

Applicants believe the instant improper abandonment is no fault of applicants; thus no fee should be charged to revive. However, to avoid this petition being dismissed, please charge the petition fee of $130 as required by 37 C.F.R. §1.17(h) to Deposit Account No. 02-2334.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional

fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly extension of time fees.

Respectfully submitted,



Mark W. Milstead
Associate Patent Counsel
Registration No. 45,825

Akzo Nobel Patent Department
Intervet Inc.
405 State Street
P.O. Box 318
Millsboro, DE 19966
Tel: (302) 934-4395
Fax: (302) 934-4305

Enclosure:
37 C.F.R. §1.111 Amendment 9/16/2003
Information Disclosure Statement 9/16/2003
Response to Examiner Communication 3/10/2004
Copy of Notice of Abandonment

PTO/SB/92 (08-03)
Approved for use through 07/31/2006. OMB 0561-0031
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Certificate of Mailing under 37 CFR 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:

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P.O. Box 1450
Alexandria, VA 22313-1450

on 4/12/04 .
Date

Katrina M Meas
Signature

Katrina M Meas
Typed or printed name of person signing Certificate

USSN: 10/089542
2000.5510US

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Petition (5pgs)
Copy of NOA (4pgs)
Copy of 3/10/04 Resp to Ex Comm (5pgs)
Copy of 37 CFR 1.111 Amend (14pgs)
Copy of cited Ref (3 ref)
Auth to charge fee for Petition

Copy of
Notice of Abandonment of
4/7/2004

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,542	03/29/2002	Victor Johannes Nickolson	2000.551US	4736

31846 7590 04/07/2004

INTERVET INC
405 STATE STREET
PO BOX 318
MILLSBORO, DE 19966

EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Copy of Response to Examiner Communication of 3/10/2004

Attorney Docket NO. O/2000.551 US

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

BY: Mark W. McKenna

Date: 3/10/2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:
NICKOLSON, Victor

Serial No.:	10/089,542	Group:	1614
Filed:	March 29, 2002	Examiner:	B. Y. S. Kwon
For:	DRUG COMBINATION FOR THE TREATMENT OF HEADACHE COMPRISING A NON-STEROIDAL ANTI-INFLAMMATORY DRUG		

RESPONSE TO EXAMINER TELEPHONE COMMUNICATION

Honorable Commissioner of Patents
Alexandria, VA 22313

March 10, 2004

Sir:

In response to the telephone conversation of March 10, 2004, Applicants respectfully submit the following documents in connection with the above-identified application.

Response to June 18, 2003 Office Action

Applicants responded timely to the Office Action mailed June 16, 2003. Applicants mailed an Amendment under 37 C.F.R. §1.111 and an Information Disclosure Statement on September 16, 2003. Applicants have attached these documents to this communication.

In addition, Applicants have attached the Certificate of Mailing Under 37 C.F.R. §1.8 signed by Katrina Mears, Intervet Patent Department Administrator.

Applicants respectfully submit that a Response was filed timely.

Conclusion

Applicants filed the response timely and respectfully request the Examiner to consider the attached 37 C.F.R. §1.111 Amendment and Information Disclosure Statement.

If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (302) 934-4395, in Millsboro, Delaware.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional

fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly extension of time fees.

Respectfully submitted,

Mark W. Milstead
Associate Patent Counsel
Registration No. 45,825

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Patent Department
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Enclosure: 37 C.F.R. §1.111 Amendment
Information Disclosure Statement

Mark W. Milstead
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Phone: 1 302 934 4395
Fax: 302 934 4305

Intervet Inc.

Fax

To:	United States Patent and Trademark Office	**From:**	Mark W. Milstead
Fax:	703 872-9306	**Date:**	March 10, 2004
Phone:		**Pages:**	48
Re:	10/089,542	**CC:**	

☑ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

•Comments:

Re: Nickolson, Victor

10/089,542

Attorney Docket O-2000.551 US

HP OfficeJet T Series
Personal Printer/Fax/Copier/Scanner

Fax History Report for
Intervet Inc.
934 4305
Mar 10 2004 5:27pm

Last Fax

Date	Time	Type	Identification	Duration	Pages	Result
Mar 10	5:09pm	Sent	917038729306	17:11	43	OK

Result:
OK - black and white fax
OK color - color fax

Copy of
37 C.F.R. § 1.111 Amendment of
9/16/2003

Certificate of Mailing Under 37 CFR 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:

Commissioner for Patents
Alexandria, VA 22313

On: September 16, 2003

Signature _____

Typed or Printed Name KATRINA MEARS

USSN 10/089542
Docket Number O 2000.551

Postcard
Amendment (11 pages)
IDS (2 pages)
PTO 1449 (1 page)
Cited References (3)
Fee $180.00

September 16, 2003

RE: USSN 10/089542; Docket Number O 2000.551 US

Receipt is acknowledged of the papers and fees listed below in the above identified application:

Mailing Certificate (1 page)
Amendment (11 pages)
IDS (2 pages)
PTO 1449 (1 page)
Cited References (3 ref)
Fee $180.00

Attorney Docket NO. O/2000.551 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:
NICKOLSON, Victor

Serial No.:	10/089,542	Group:	1614
Filed:	March 29, 2002	Examiner:	B. Y. S. Kwon

For: DRUG COMBINATION FOR THE TREATMENT OF HEADACHE COMPRISING A NON-STEROIDAL ANTI-INFLAMMATORY DRUG

AMENDMENT UNDER 37 C.F.R. §1.111

Honorable Commissioner of Patents
Alexandria, VA 22313

September 16, 2003

Sir:

In response to the outstanding Office Action mailed June 18, 2003, Applicants respectfully submit the following amendments and remarks in connection with the above-identified application.

In the Claims

1. (Previously Amended) A pharmaceutical composition, comprising:

paracetamol or a non-steroidal anti-inflammatory drug, or a pharmaceutically acceptable salt or solvate thereof,

mirtazapine, or a pharmaceutically acceptable salt or solvate thereof, and

optionally in association with one or more pharmaceutically acceptable carriers.

2. (Previously Amended) The pharmaceutical composition according to claim 1, wherein said non-steroidal anti-inflammatory drug is selected from the group consisting of aceclofenac, antipyrine, acetylsalicylic acid, benoxaprofen, butibufen, caprofen, celecoxib, diclofenac, dipyrone, etodolac, flosulide, flurbiprofen, FR 140423, ibufenac, ibuprofen, indomethacin, ketoprofen, ketorolac, lornoxicam, loxoprofen, lysine clonixinate, M-5011, meclofenamic acid, meloxicam, metiazinic acid, nabumetone, naproxen, NS-398, numesulide, oxyphenbutazone, D-penicillamine, phenylbutazone, piroxicam, pyrazolone, rofecoxib, salsalate, salicylate, SC-58236, SC58560, sulfasalasine, sulindac, tiaprofenic acid, tenidap, tenoxicam, tepoxalin, tolfenamic acid, tolmetin and zaltoprofen.

3. (Currently Amended) The pharmaceutical composition

according to claim 2, wherein said non-steroidal anti-inflammatory drug is ~~ibuprofen~~ ibuprofen.

4-8. (Canceled)

9. (Previously Amended) A method for treating a headache in a subject, comprising:

administering to said subject an effective amount of mirtazapine in combination with paracetamol or a non-steroidal anti-inflammatory drug.

10. (Previously Amended) A method of treating a headache in a subject according to claim 9, wherein the amount of mirtazapine is between 0.1 and 5 mg.

11. (Previously Amended) The method of treating a headache in a subject according to claim 9, wherein the headache is a tension-type headache.

12. (Previously Amended) A patient pack for the treatment of a headache, comprising:

means for administration of metered dose units in combination with packaging material suitable for said dose units, wherein the patient pack comprises mirtazapine, and paracetamol or a non-steroidal anti-inflammatory drug, and optionally, said

packaging material is including means to help a recipient using the dose units most suitably for the treatment of a headache.

13. (Previously Amended) The patient pack according to claim 12, wherein the dose units comprise pharmaceutical auxiliaries and mirtazapine in an amount between 0.1 and 5 mg.

14. (Previously Added) A method of treating a headache in a patient, comprising:

administering an effective amount of the pharmaceutical composition according to claim 1.

15. (Previously Added) The method according to claim 14, wherein the effective amount of the pharmaceutical composition comprises about 0.1 to 5 mg of mirtazapine.

16. (Previously Added) The method according to claim 14, wherein the headache is a tension-type headache.

17. (Previously Added) The method according to claim 14, wherein the effective amount of the pharmaceutical composition comprises about 0.1 to 5 mg of mirtazapine and wherein the non-steroidal anti-inflammatory drug is ibuprofen.

18. (NEW) The pharmaceutical composition of claim 1, wherein

mirtazapine is chiral S(+) enantiomer.

19. (NEW) The method of claim 9, wherein mirtazapine is chiral S(+) enantiomer.

REMARKS

Upon entry of the above amendment, claims 1-3 and 9-19 will be pending. Claims 1, 9, and 12 are independent claims.

Applicant has amended claim 3 to correct a typographical error. The specification on page 3 provides support for new claims 18 and 19. Applicant has not raised any issue of new matter.

Priority

The Examiner asserts that Applicant has not filed a certified copy of the EP 00201239.1 application as required by 35 U.S.C. §119(b). Applicant has filed the proper documents with WIPO. Applicant has attached a copy of Form PCT/IB/304 that indicates that Applicant has filed the priority document on July 9, 2001.

Applicant respectfully requests the Examiner to WIPO to send a copy of the priority document.

Issue Under 35 U.S.C. §103(a)

Claims 1-3 and 9-17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lange et al (Drugs under Experimental and Clinical Research, 1995, 21(3), 89-96) in view of Olsen '674

(WO 9819674). Applicant asserts that patentable distinctions exist between the cited prior art and the present invention.

Distinctions Between the Present Invention and Lange et al in view of Olsen '674

Lange et al discloses the safety and efficacy of treatment of tension-type headache with either ketoprofen or ibuprofen. Lange et al. fails to disclose a pharmaceutical combination of a NSAID with any other pharmaceutical compound.

Olsen '674 discloses on page 32, lines 7-13 that mirtazapine "may also have an effect on glutamine neurotransmission, potentially as non-competitive NMDA receptor antagonists. It is through this mechanism that [mirtazapine is] presumed to provide a method of treatment of tension-type headaches." The only demonstrated anti-headache effects in Olsen '674 are with L-NMMA (page 74-75), Gabapentin (page 91) and Dextromethorphan (page 93). Olsen '674 provides no mechanistic or structural relation between the exemplified drugs and mirtazapine.

Olsen '674 fails to provide any data to support its assertion; therefore, Olsen '674 is merely speculating as to the action of mirtazapine and many other compounds. For example as to the speculation within Olsen '674, Applicant directs the Examiner to speculative claim 14 where Olsen '674 appears recite every possible mechanistic relationship without any support. More importantly, Olsen '674 fails to disclose any combination

composition for treatment of headaches containing mirtazapine and a NSAID.

The Examiner asserts that a skilled artisan would combine the two cited references to render the present invention obvious because both compounds are "known" treatments of tension-type headaches. As indicated above, Olsen '674 only speculates that mirtazapine might provide a treatment, but provides no actual support for its assertion. Neither reference discloses or suggests combination treatments with mirtazapine. In addition, neither reference suggest the dosage range of 0.1 to 5mg as claimed in claims 10, 13, 15 and 17.

The Examiner must present a *prima facie* case of obviousness consisting of motivation or suggestion to modify or combine references such that one of ordinary skill in the art has a reasonable expectation of success of making the present invention. "To prevent the use of hindsight **based on the invention** to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and **with no knowledge of the claimed invention**, would select the elements from the cited prior art references for combination in the manner claimed. In re Rouffet, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-58 (Fed. Cir. 1998).

Clearly, cited prior art fails to motivate a skilled artisan to make the present pharmaceutical combination of mirtazapine and a NSAID.

Applicant respectfully requests withdrawal of the 35 U.S.C. §103(a) rejection.

Concurrently Filed Information Disclosure Statement

Applicant has filed an IDS concurrently with this amendment and remarks. Applicant believes that these references are not relevant as to the patentablity of the present application. Two of the references are self-explanatory. The Demling reference is in German and discusses mainserin andd its efficacy against tension headaches. See page 72, left column "war Mianserin gegen Spannungskopfschmerzen." Mirtazapine is discussed as a related compound, but it is stated that there is considerable distinction in pharmacological properties. See page 72, middle column "ein erheblicher Unterschied zwischen beiden Verbindungen in der Verteilung der Elektronediche und damit auch in den pharmkologischen Eigenschaften." Applicants can prepare an English translation, if the Examiner deems it necessary.

Conclusion

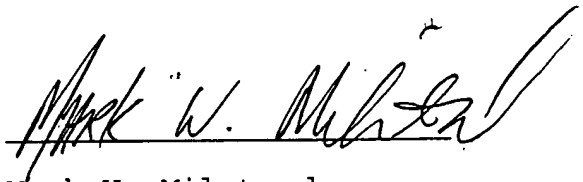
All the stated grounds of the rejections have been properly traversed, accommodated or rendered moot. Applicant respectfully submits that the present application is in condition for

allowance.

If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (302) 934-4395, in Millsboro, Delaware.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly extension of time fees.

Respectfully submitted,



Mark W. Milstead
Associate Patent Counsel
Registration No. 45,825

Attorney Docket NO. O/2000.551 US

Intervet Inc.
Patent Department
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MWM

Enclosure: Form PCT/IB/304

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

12 OKT. 2001

KRAAK, H.
P.O. Box 20
NL-5340 BH Oss
PAYS-BAS

Date of mailing (day/month/year) 25 September 2001 (25.09.01)	
Applicant's or agent's file reference 2000.551 WO	IMPORTANT NOTIFICATION
International application No. PCT/EP01/04069	International filing date (day/month/year) 04 April 2001 (04.04.01)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 05 April 2000 (05.04.00)
Applicant AKZO NOBEL N.V. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
05 Apri 2000 (05.04.00)	00201239.1	EP	09 July 2001 (09.07.01)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

David MALEK

Telephone No. (41-22) 338.83.38

Copy of
Information Disclosure Statement
of 9/16/2003

Attorney Docket Number O 2000.551 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

NICKOLSON, Victor

Serial No.: 10/089,542 Group Art Unit: 1614

Filed: March 29, 2002 Examiner: B.Y.S. Kwon

For: DRUG COMBINATION FOR THE TREATMENT OF HEADACHE COMPRISING A NON-STEROIDAL ANTI-INFLAMMATORY DRUG

Corresponding to: PCT/EP01/04069, filed April 4, 2001

INFORMATION DISCLOSURE STATEMENT AND TRANSMITTAL OF FEE PURSUANT TO 37 CFR 1.97(c)

Assistant Commissioner of Patents
Washington, D.C. 20231 September 16, 2003

Sir:

The attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached Form PTO-1449. One copy of each of these documents is attached.

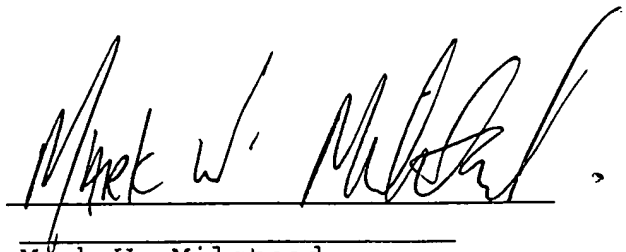
This Information Disclosure Statement is being submitted after issuance of a first official action on the merits and expiration of the three month period following filing of the above-captioned application, but prior to issuance of either a final official action or a Notice of Allowance. The $180.00 fee set forth in 37 CFR Section 1.17(p) may be charged to Deposit Account No. 02-2334

The above information is presented so that the Patent and Trademark Office can determine any materiality thereof to the claimed invention. It is respectfully requested that the

information be expressly considered during the prosecution of this application.

The Commissioner is hereby authorized to charge any additional fee (or credit any overpayment) associated with this statement to our Deposit Account No. 02-2334.

Respectfully submitted,



Mark W. Milstead
Attorney for Applicants
Registration No. 45,825

Intervet Inc Patent Department
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INFORMATION DISCLOSURE CITATION PTO-1449	Attorney Docket No. O 2000.551	Serial No. 10/089,542
	Applicant NICKOLSON, Victor	
	Filing Date March 29, 2002	Group 1614

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Translation
	AJ				
	AK				
	AL				
	AM				
	AN				
	AO				
	AP AQ				

OTHER DOCUMENTS

	AR	**GREENSHAW ET AL**: "The Non-Antiemetic Uses of Serotonin 5-HT3 Receptor Antagonists Clinical Pharmacology and Therapeutic Applications"; Drugs, January 1997, (53) 1; pages 20-39
	AS	**DEMLING, J**: "Tetrazyklische Antidepressiva: Pharmakologisch-klinische Aspekte und Neuentwicklungen";Nervenheilkunde 1996: 15:92-100
	AT	**LIEH ET AL**: "Mechanism of Action of the Antidepressant Mirtazapine"; Abstracts of the 10th World Congress of Psychiatry, Madrid, August 23-28, 1996, S.l., s.n., 1996; 2:302
	AU	
	AV	

Examiner	Date Considered

REVIEW ARTICLE

Drugs 1997 Jan; 53 (1): 20-30
0012-6667/97/0001-0020/$20.00/0

The Non-Antiemetic Uses of Serotonin 5-HT$_3$ Receptor Antagonists

Clinical Pharmacology and Therapeutic Applications

Andrew J. Greenshaw and *Peter H. Silverstone*

Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada

Contents

Summary

The discovery of multiple subtypes of the serotonin 5-HT receptor has generated enormous interest over the past few years. Possibly the most exciting, in terms of psychiatric clinical practice, appeared to be the 5-HT$_3$ receptor. Early animal studies suggested that the 5-HT$_3$ receptor antagonists, in addition to their well recognised antiemetic use, might be clinically useful in a number of areas. These included anxiety disorders, psychotic disorders, drug and alcohol abuse disorders, depressive disorders, cognitive disorders, the treatment of pain and the treatment of irritable bowel syndrome. With the exception of antiemetic actions, this review examines these potential therapeutic areas carefully, paying particular attention not only to the animal literature, but to the clinical studies which have resulted from these initial findings. Unfortunately, studies in many of these therapeutic areas have not lived up to their initial promise. Indeed, no clinical studies have yet clearly demonstrated the usefulness of 5-HT$_3$ receptor antagonists in the treatment of CNS disorders. Nonetheless, in view of the absence of published results from double-blind, placebo-controlled studies in many of these therapeutic areas, further research would be useful in confirming the effectiveness, or otherwise, of this group of compounds.

There have been many proposals for therapeutic applications of drugs that are antagonists at the recently cloned serotonin 5-HT$_3$ receptor.[1-6] The range of the postulated therapeutic potential of these compounds is vast, although their demonstrated clinical efficacy currently remains limited to antiemetic actions.[7,8] The promise of these drugs lies in the fact that they appear to have few or no adverse effects in the clinic.

Numerous preclinical reports have suggested

that 5-HT$_3$ receptor antagonists (fig. 1) may be effective for the treatment of a variety of disorders, particularly psychiatric disorders. The diseases that have been targeted for development of these drugs have included: schizophrenia, anxiety disorders, syndromes of memory impairment that accompany dementia, substance abuse, depression, migraine and, last but not least, irritable bowel syndrome.

The purpose of the present report is to summarise the evidence for potential clinical uses of the 5-HT$_3$ receptor antagonists. The role of these compounds as useful antiemetics is not discussed in any detail here as this action is well established and has been described.

The excitement that arose when the 5-HT$_3$ receptor was first identified in the mammalian brain[9] and when the unique pharmacological properties of this receptor were revealed[10] provided a tremendous initial burst of research activity. The 5-HT$_3$ receptor is now quite firmly established as a regulator of neural function. This receptor stands apart from other known 5-HT receptor subtypes as it resembles receptors of the nicotinic acetylcholine receptor family[10] (table I). The 5-HT$_3$ receptor gates a membrane ion channel that conducts monovalent cations such as Na^+ and K^+ but excludes anions.[11]

It has been suggested that as many as 3 subtypes of this 5-HT$_3$ receptor may be expressed.[12] This has yet to be confirmed, although there are definite structural and functional differences both within and between species.[13-15] Current evidence indicates that this receptor exhibits the pentameric structure characteristic of ligand-gated ion channels.[16] In terms of pharmacological investigation, the 5-HT$_3$ receptor also stands out from other 5-HT receptors in terms of ligand selectivity. Numerous compounds have been identified as highly selective 5-HT$_3$ receptor antagonists which readily cross the blood-brain barrier. The high selectivity of these compounds, together with their typically high potency and apparent lack of adverse effects, have made these drugs excellent candidates for potential pharmaceutical drug development.

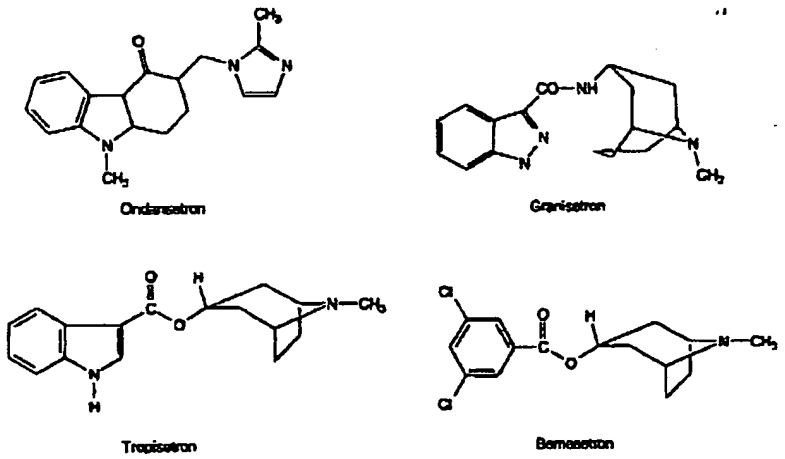


Fig. 1. Structural formulas of selected serotonin 5-HT$_3$ receptor antagonists.

Table I. Serotonin 5-HT receptor subtypes[5]

Name	Selective agonists	Selective antagonists	Transduction mechanism	Molecular identification (species (chromosome))
5-HT_{1A}	8-OH-DPAT	WAY-100635	cAMP (–), K^+ channel (+)	Human, mouse (13), rat
5-HT_{1B}	CP-93129		cAMP (–)	Mouse, rat
5-HT_{1Da}	Sumatriptan		cAMP (–)	Human (1), rat, dog
$5\text{-HT}_{1Dβ}$	Sumatriptan		cAMP (–)	Human (6)
5-HT_{1E}			cAMP (–)	Human, mouse, rat
5-HT_{1F}			cAMP (–)	Human, mouse, rat
5-HT_{2A}	αMeS-HT	Ketanserin	IP3/DG (+)	Human (13), mouse (14), hamster
5-HT_{2B}	αMeS-HT	LY-053857	IP3/DG (+), Cl^- channel (+)	Human, mouse, rat
5-HT_{2C}	αMeS-HT	Mesulergine	IP3/DG (+), Cl^- channel (+)	Human (X), mouse (X), rat
5-HT_3	2MeS-HT	Tropisetron	Na^+/K^+ internal channel (+)	Rat
5-HT_4	5-MT	GR-113808	cAMP (+)	Not cloned
5-HT_{5A}			Not known	Mouse, rat
5-HT_{5B}			Not known	Mouse, rat
5-HT_6			cAMP (+)	Rat
5-HT_7			cAMP (+)	Human, rat

Abbreviations: 5-MT = 5-methoxytryptamine; cAMP = cyclic adenosine monophosphate; IP3/DG = inositol trisphosphate/diacylglycerol; MeS-HT = methyl-serotonin.

Selective 5-HT_3 receptor agonists (fig. 2), such as *m*-chlorophenylbiguanide,[17] have been identified, but most of these compounds do not cross the blood-brain barrier, and this has limited studies with these drugs. The recent discovery of a range of novel 1-heteroaryl-4-alkyl-4-amino-piperidines (such as SR 57227A) which readily cross the blood-brain barrier and exhibit high potency and selectivity as agonists at the 5-HT_3 receptor represents a significant advance in this area.[18] Nevertheless, since the discovery of the putative 5-HT_4 receptor it is evident that some 5-HT_3 receptor antagonists such as tropisetron and renzapride may also have 5-HT_4 receptor–related activity.[19]

To date, there has been little attempt to provide a realistic critical evaluation of the growing literature on 5-HT_3 receptor pharmacology in the therapeutic context.[20] It is now clear that there is very little clinical support for many of the proposals generated by early preclinical studies. In addition, the preclinical research concerning these compounds has not yielded a clear view of their actions in many areas of potential application.

1. Pharmacotherapy of Anxiety Disorders

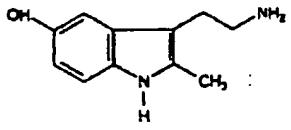
One property of many putative anxiolytic drugs is their ability to reduce behavioural inhibition due to aversive conditioning in some tests. Di Chiara's group[21] reported the blockade of acquisition of a drug-conditioned place-aversion by 5-HT_3 receptor antagonists. In such experiments, pairing of a drug (naloxone, phencyclidine or picrotoxin) with the preferred compartment of a 2-compartment apparatus may elicit a significant shift in preference (aversion). Both tropisetron and bemesetron blocked the acquisition of place aversions induced by these compounds. In an earlier study,[22] diazepam and tropisetron were both shown to inhibit expression of a conditioned place-aversion elicited by footshock.

Such results may indicate anxiety-reducing effects of 5-HT_3 receptor antagonism. Nevertheless, aversive responses to electrical stimulation of the dorsal periaqueductal grey region of the midbrain are unaffected by 5-HT_3 receptor antagonism.[23] Paradoxically, this implies no influence of 5-HT_3

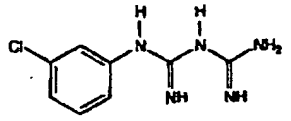
receptor antagonism on central systems mediating aversive responses.

More recently, the effects of 5-HT$_3$ receptor antagonism on establishment of conditioned taste aversions induced by nicotine have been examined; no attenuation of the nicotine response was observed. In this study, 5-HT$_3$ antagonism resulted in the reduction of a taste preference, indicating at least some aversive consequences of 5-HT$_3$ receptor blockade.[24]

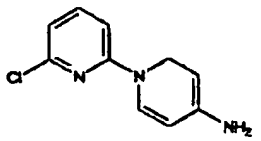
Various studies indicate the potential for anxiety-reducing effects of 5-HT$_3$ antagonists in animal models.[25] Such studies have included the black : white 2-compartment test (in which rodents' increased time in the white compartment is taken to indicate an anxiolytic effect); Sandra File's social interaction test (in which increased social interaction between two unfamiliar rodents is taken to indicate an anxiolytic effect); and the marmoset human-threat test. In the latter test, changes in both the body postures and the retreat to the rear of the cage which are normally induced by the presence of a human are indicative of anxiolytic action. In contrast to reports of positive anxiolytic responses to 5-HT$_3$ receptor antagonists such as zacopride, ondansetron, granisetron and tropisetron with these procedures, such compounds usually test negatively in conflict or punishment tests such as the Vogel conflict test: suppression of water-licking subsequent to unavoidable shock.[25]



2-Methyl-serotonin



m-Chlorophenylbiguanide



SR 57227A

Fig. 2. Structural formulae of selected serotonin 5-HT$_3$ receptor agonists.

Griebel[26] has reviewed the efficacy of serotonin-related drugs in laboratory animal tests for anxiolytic effects quite extensively and has provided a very useful discussion of this area in a more general context: the reader is referred to this source for a discussion of the possible mismatch between the results of laboratory animal tests and of clinical studies.

Although research on anxiolytic actions of these compounds has been extended to localisation of the possible central site of action to the amygdala,[27] it is evident that some researchers have failed to observe anxiolytic actions of these compounds in the elevated plus-maze test (a plus-shaped maze with 2 open and 2 closed arms somewhat analogous to the black : white 2-compartment test).[28] Anxiolytic effects of these compounds have been observed neither in the social interaction test with high levels of social interaction in control animals[29] nor with socially isolated rats placed in a light : dark shuttlebox.[30]

Andrews and File[31] have demonstrated that procedural differences may account for some of the discrepancies in preclinical anxiolytic testing with models such as the elevated plus-maze. In this study the handling history of animals 'blocked' the 'anxiolytic' effects of zacopride and shifted the dose-response to the right for baclofen. This result has important implications for the interpretation of 'anxiolytic' drug effects with respect to between-laboratory differences with the plus-maze and possibly other tests.

Gao and Cutler,[32] using ethological methods with mice and gerbils, have observed effects which

have been interpreted as consistent with anxiolytic action. Further positive evidence has been published comparing the novel 5-HT_3 antagonist WAY 100289 to ondansetron, zacopride and tropisetron using the light : dark box and an acoustic startle procedure.[33] In addition, the novel 5-HT_3 receptor antagonist ricasetron (BRL 46470A) was recently shown to be 100 times more potent than ondansetron and was active in the elevated plus-maze and the social interaction test.[34] This compound is apparently devoid of the bell-shaped dose-response curve that has made choice of test dose so complex an issue for compounds such as ondansetron.[34]

The difference between the dose-response function for ricasetron and other 5-HT_3 receptor antagonists has been the focus of interest for generating other selective 5-HT_3 receptor antagonists that may be devoid of the bell-shaped dose-response profile of drugs such as ondansetron, bemesetron and granisetron. In an analysis of the receptor binding profile of [^{3}H]ricasetron, Steward et al.[35] have demonstrated that this ligand appears to label a higher density of specific 5-HT_3 receptor sites than [^{3}H]granisetron (using ondansetron to define 5-HT_3 receptor binding) in various tissue preparations. The inability of [^{3}H]ricasetron to label the 5-HT_3 receptors expressed in human putamen[35] emphasises the importance of inter-species differences in 5-HT_3 receptor binding.[15]

Nevins and Anthony[36] have evaluated the ability of 5-HT_3 receptor antagonists to reduce the fear-potentiated startle response in rats. These authors report that these compounds are only effective in this test when a relatively low shock intensity is used during training. This is consistent with the idea that only relatively low levels of (experimentally defined) fear or anxiety are affected by 5-HT_3 receptor antagonists.[36] Neither the anxiogenic nor the discriminative stimulus effects of pentetrazol (pentylenetetrazol) are affected by 5-HT_3 receptor blockade with ondansetron, which is the most widely studied 5-HT_3 receptor antagonist in this context.[28]

Recently, Olivier et al.[37] have examined the actions of a variety of putative anxiolytic drugs in two new animal models: stress-induced hyperthermia in mice and ultrasonic pup vocalisations in rats. 5-HT_3 receptor antagonists were inactive in these tests in contrast to other well established anxiolytics.

In a review of work related to aggression, anxiety and vocalisations in laboratory animals, Miczek et al.[38] have stated that 5-HT_3 receptor antagonists suppress aggressive behaviour with limited specificity. Despite inconsistencies in the findings from anxiolytic testing (also, see Olivier et al.[39]) there appears to be some agreement for alleviation of apparent anxiogenic effects of benzodiazepine withdrawal by 5-HT_3 receptor antagonists.[25,28,40] Nevertheless, at least one study indicates that 5-HT_3 receptor antagonists are ineffective in attenuating hyperlocomotor activity following abrupt termination of long term administration of alcohol (ethanol) or diazepam.[41] In addition, these compounds may be ineffective in attenuating the increased sensitivity to pentetrazol in alcohol-withdrawn rats.[41]

Although the 5-HT_3 receptor antagonists may alleviate the apparent anxiogenic effects of benzodiazepine withdrawal they may only be only partially effective (ondansetron) or ineffective in alleviating the anorexia or weight loss in this context.[42] In terms of physiological responses it is interesting to note that stimulation of 5-HT_3 receptors may result in an increase in adrenocortical secretion in male rats, an effect which is associated with animal models of stress or anxiety.[43] The increase in plasma corticosterone levels in this study were attenuated by 5-HT_3 receptor antagonism with bemesetron[43] (but contrast this result with the human volunteer study of Silverstone and Cowen[44]).

At the neuronal level it is of interest that 5-HT_3 receptors have been implicated in regulation of central cholecystokinin (CCK) release.[45] Endogenous CKK is currently an important focus of interest in relation to anxiety in the aetiology and treatment of panic disorder, as this neuropeptide is an anxiogenic agent.[46] Stimulation of 5-HT_3 receptors may be associated with release of cortical

and limbic CKK as the 5-HT_3 receptor antagonists ondansetron, bemesetron and tropisetron reduce CKK-like immunoreactivity.[45]

At the clinical level, few data are available describing anxiolytic actions of 5-HT_3 antagonists. A study[25] of ondansetron for the treatment of generalised anxiety disorder has yielded some marginal results: Hamilton Anxiety Rating Scale scores indicated that ondansetron was as effective as diazepam but each treatment group was only slightly (57 to 59%) higher in treatment response than placebo (45%). Using the Montgomery-Åsberg Depression Rating Scale the ondansetron response (54 to 59%) was marginally higher than the diazepam response (51%) or placebo. The rather high relative placebo effect in this study is clearly problematic.

The effects of ricasetron on 'panic' induced by the serotonin agonist *m*-chlorophenylpiperazine (*m*-CPP) have been investigated in an attempt to assess the possible efficacy of 5-HT_3 antagonism in panic disorder. Ricasetron did not attenuate any panic symptoms in this study.[46] Nevertheless, in a randomised double-blind placebo-controlled trial, Lecrubier and colleagues[47] reported an anxiolytic effect of tropisetron in patients with generalised anxiety disorder. This statistically significant effect was dose-related in male patients and was detected after 7 days of treatment.

Although there are considerable amounts of preclinical data concerning potential anxiolytic effects of 5-HT_3 antagonists, the clinical evidence is, as yet, far from compelling. What is needed is a series of independent placebo-controlled trials in patients with anxiety disorder. Up to the present time, several 5-HT_3 receptor antagonists have been in clinical trials for anxiolytic action.[48] So far, there have been no signs of strong contenders in this group of drugs for the clinical management of anxiety and related disorders.

2. Antipsychotic Effects

The earliest behavioural studies indicating central actions of 5-HT_3 antagonists used procedures sensitive to actions of established antipsychotic drugs.[49,50] Ondansetron injected intraperitoneally or into the nucleus accumbens of the forebrain inhibited hyperlocomotion induced by intra-accumbens injections of dexamphetamine in rats. Under similar conditions the stimulant effects of peripherally administered amphetamine were unaffected. In other experiments, ondansetron injected intraperitoneally 2 or 3 times daily abolished hyperlocomotion induced by withdrawal from long term infusion of dopamine into the nucleus accumbens in rats or marmosets (anterior ventromedial striatum).

Initial studies had revealed 5-HT_3 antagonists to be devoid of classical neuroleptic effects such as catalepsy, antagonism of stereotyped behaviour or inhibition of conditioned avoidance at doses that completely blocked the von Bezold-Jarisch reflex.[51] The rather selective profile of action against mesolimbic dopamine-related hyperactivity was initially very exciting as it suggested the possibility of developing a novel class of antipsychotics which would be devoid of the motor adverse effect profile of standard compounds.

Subsequent studies using other procedures have yielded interesting results, but there are clear problems of interpretation for these preclinical findings. Ostensibly, 5-HT_3 antagonists have no effect on 'normal' levels of behavioural output (e.g. basal locomotor activity) or changes in behaviour related to activity of the nigrostriatal dopamine system (e.g. stereotypy following peripheral amphetamine or apomorphine), whereas they may selectively inhibit behaviours associated with stimulation of the mesocorticolimbic dopamine system.

This proposal has some support from studies of effects of 5-HT_3 antagonists on the actions of drugs which induce increased dopamine cell-firing in the ventral tegmental area (and consequently increase dopamine release in the nucleus accumbens). An early study demonstrated that hyperactivity following administration of a stable substance P analogue into the ventral tegmental area may be attenuated by 5-HT_3 receptor antagonism.[6,52,53] The 5-HT_3 receptor agonist 1-phenyl-biguanide has been reported to increase amphetamine-induced

activity in rats, an effect which was partially attenuated by the 5-HT_3 receptor antagonist bemesetron.[54] However, the effects of this agonist are now known to be partially attributable to direct actions on the dopamine transporter.[17,55]

The rewarding effects of nicotine and morphine in conditioned place preference conditioning (the inverse of place-aversion conditioning) are apparently abolished by 5-HT_3 receptor antagonists.[56,57] Microdialysis studies have indicated that these compounds also block the increase in nucleus accumbens dopamine release induced by these rewarding drugs. Indeed, one study reports abolition of grooming induced by nicotine and a concomitant decrease in release of dopamine from this area following administration of a 5-HT_3 receptor antagonist.[58]

Electrophysiological studies indicate that the decrease in stimulated dopamine release induced by 5-HT_3 receptor antagonists may not be due a decrease in the drug-stimulated firing rates of dopamine-containing cells in the ventral tegmentum.[59] Studies of effects of 5-HT_3 receptor antagonists on spontaneous firing rates of these ventral tegmental neurons have yielded mixed results,[60-62] possibly due to the heterogeneity of the actions of these drugs on 5-HT_3 receptors[15] and/or their interaction with more recently characterised 5-HT receptor subtypes such as the 5-HT_4 receptor.[19]

The effects of 5-HT_3 receptor antagonists on stimulated dopamine release and related behaviours described above have not been consistently supported by other studies. Arnold et al.[24] failed to observe any effect of ondansetron or bemesetron on the hyperactivity induced by repeated intermittent administration of nicotine. This hyperactivity effect was attenuated by the nicotine antagonist mecamylamine and by the dopamine D_2 receptor antagonist haloperidol. Pei et al.[63] and Moser[64] have reported a similar lack of selective 5-HT_3 receptor antagonist effects in this context (but see Volonté et al.[65] and Geissler et al.[66]).

Several other studies investigating effects of 5-HT_3 receptor antagonism on rewarding effects of electrical brain self-stimulation or rewarding drug effects believed to be mediated by dopamine release in the nucleus accumbens have failed to support the proposed selective actions of these compounds on stimulated dopamine release in this region.[67-72] In the studies of ventral tegmental self-stimulation, repeated administration (once or twice daily) of ondansetron failed to alter reward thresholds.[73] Koulu et al.[74] have also reported that repeated administration of ondansetron does not result in a reduction of mesolimbic (or nigrostriatal) dopamine activity in terms of metabolism or receptor binding. In addition, 5-HT_3 receptor antagonists do not appear to influence the reward-enhancing effects of nicotine[70,72] or the CCK analogue ceruletide (caerulein)[69] on behaviour maintained by rewarding electrical brain stimulation. Cocaine self-administration in laboratory animals and the discriminative stimulus effects of cocaine are also reported to be unaffected by 5-HT_3 receptor antagonism.[71]

One interesting and potentially important observation is the ability of 5-HT_3 receptor antagonists such as bemesetron and granisetron to inhibit catalepsy induced by haloperidol in rats.[75] This has been an area of focus for compounds that interact with 5-HT_{1A} receptors,[76] and further reports in this area will be of interest.

The early preclinical optimism for antipsychotic potential of these compounds has been dampened both by these subsequent preclinical studies and by the paucity of clinical data indicating any antipsychotic effects of 5-HT_3 antagonists. Although there are case reports and open trials of positive effects (e.g. see White et al.[77]), no double-blind placebo controlled trials have yet emerged with positive responses.[78] One single-blind trial of zacopride indicates no clinical benefit in the treatment of acute schizophrenia.[79] Results from double-blind placebo-controlled studies with ondansetron have been negative.[80]

Many of the data from clinical trials remain unpublished and it is apparent that some pharmaceutical companies have already withdrawn this class of compounds from trials in this area. One intri-

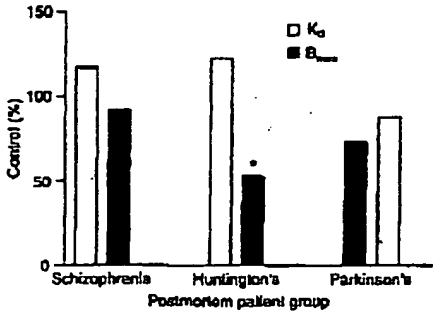


Fig. 3. Despite a postulated role for serotonin 5-HT$_3$ receptors in the pathophysiology and treatment of schizophrenia, no changes in receptor affinity (K_d) or density (B_{max}) have been observed for human postmortem brain analysis of schizophrenic or parkinsonian patients. A reduction in the density of these receptors has been reported from postmortem analysis of brain tissue from patients with Huntington's disease.[82,83]

guing report of a short term open trial of ondansetron for treatment of psychosis in Parkinson's disease is positive.[81] In this study, ondansetron was claimed to be beneficial for the treatment of patients with advanced Parkinson's disease. The drug was well tolerated and, as expected, induced no major adverse effects.

In view of the balance of available evidence it seems unlikely that 5-HT$_3$ receptor antagonists will prove to be effective antipsychotics in the foreseeable future. On a purely academic note it is of interest that from postmortem analyses, the density of 5-HT$_3$ receptors in the human amygdala is unaltered in schizophrenic patients (fig. 3).[82] In contrast to this result, Steward et al.[83] have reported reduced levels of these 5-HT$_3$ receptor recognition sites in the putamen in postmortem analysis of brain tissue from patients who had Huntington's disease (fig. 3).

3. Pharmacotherapy of Drug Abuse and Appetite Disorders

Blockade of conditioned place-preferences to morphine, nicotine and 3,4-methylenedioxy-methamphetamine (MDMA; 'Ecstasy') by 5-HT$_3$ antagonists has been interpreted as evidence for possible use of these compounds in the treatment of drug abuse.[56,57,84] It is notable that although 5-HT$_3$ receptor antagonists are reported to attenuate locomotor activity induced by cocaine in mice,[85] the rewarding effects of dexamphetamine, nicotine and cocaine are unaffected by these compounds in rats, as are their discriminative stimulus properties.[71,86-90]

There is some evidence that the neurochemical correlates of continuous cocaine administration in rats involve an alteration of 5-HT$_3$ receptor-mediated effects.[91] Nevertheless, these results do not have obvious implications for a role of this receptor in cocaine abuse as the relevant pattern of drug exposure is intermittent.

One pilot study in human volunteers revealed a decrease in subjective responses to amphetamine following ondansetron; this was not mood-related and the authors were unable to exclude a pharmacokinetic interaction to explain the effect.[92] A preliminary report has also suggested that the subjective effects of cocaine may be attenuated by ondansetron[93] – this result has not yet been confirmed.

In relation to opiate drugs there is substantial evidence indicating a 5-HT$_3$ receptor-mediated blockade of rewarding effects of morphine in the conditioned place-preference paradigm[56,57,94] and with morphine self-administration in rats.[95] However, with intravenous self-administration of diamorphine (heroin), 5-HT$_3$ receptor antagonists (ondansetron and bemesetron) are apparently ineffective.[96] 5-HT$_3$ receptor antagonists are also ineffective in blocking the discriminative stimulus properties of morphine.[97]

A recent innovative study by Sell et al.[98] examined the effects of ondansetron on opiate-craving in addicts stably maintained on a methadone treatment programme. These individuals experienced significant craving, dysphoria and withdrawal-like symptoms when exposed to a video containing drug-related cues. Ondansetron had no effect on these symptoms. In addition, it is apparent that ondansetron may not reduce cigarette smoking in humans.[99]

There is some evidence indicating a role for 5-HT_3 receptor antagonism in decreasing alcohol intake in animal studies and in humans.[100,101] In contrast, 5-HT_3 receptor antagonists may have no effect on consumption of water and saline in laboratory animal tests.[102] In attempting to determine the mechanisms of 5-HT_3 receptor antagonist effects on alcohol consumption in alcohol-preferring rats Jankowska et al.[103] have reported that serotonin denervation by neurotoxin lesions did not reduce the alcohol intake–reducing effects of tropisetron. These authors have suggested that the 5-HT_3 receptors that may mediate the tropisetron effects are postsynaptic to serotonin neurons. The effects of these compounds on alcohol intake may possibly represent a clinically meaningful phenomenon.

Sellers et al.[104] examined the effects of ondansetron in the treatment of alcohol-dependent men. In this randomised placebo-controlled study, reductions in drinking were evident but not statistically significant at 7 weeks. When patients drinking >10 drinks per day at baseline were excluded from the analysis significant reductions in drinking were evident, during ondansetron treatment and at follow-up. Lower baseline drinking and a higher level of education were significant predictors of drinking reduction during treatment.

Johnson and Cowen[105] have reported preliminary findings that indicate a reduction in the pleasurable effects of a small dose of alcohol and a concomitant reduction in the desire to drink following administration of ondansetron. A more detailed study by Doty et al.[106] did not reveal any effect of ondansetron on subjective responses to alcohol in a similar context. These authors point out that they used a different alcohol dose from that used by Johnson and Cowen,[105] and conclude that the utility of ondansetron in treating alcohol abuse may be quite limited if it is only efficacious in blocking the actions of a low dose of alcohol. This latter point has implications for the interpretation of the results of Sellers et al.[104]

In addition, in a recent preclinical study the 5-HT_3 receptor antagonist bemesetron was reported to *exacerbate* alcohol withdrawal seizures in mice, although tropisetron was without effect.[107] This result is directly counter to what may be predicted for a compound that may be useful for the alleviation of symptoms of alcohol abuse. There has been a contrasting report,[108] in which tropisetron reduced alcohol preference and reduced seizures in alcohol-withdrawn rats. In the former study seizures were induced by handling whereas in the latter study they were audiogenic.

These findings indicate a lack of consistency in responses to 5-HT_3 receptor antagonists, a pattern that is evident in other areas of research. A further result that may reduce confidence in this area in terms of prospective pharmacotherapy is the failure of 5-HT_3 receptor antagonists to alter alcohol self-administration with rats responding on an operant (fixed ratio) self-administration schedule.[109]

The effects of 5-HT_3 receptor antagonists on rewarding actions of drugs are not general. In the context of pharmacotherapy of drug abuse perhaps treatment of the anxiogenic effects of benzodiazepine withdrawal may represent a useful role for 5-HT_3 antagonists.[25,28,40]

In terms of influences on behaviour of an appetitive nature there has been some analysis of effects of 5-HT_3 receptor antagonists on sexual behaviour and on feeding. Tanco et al.[110] examined effects of ondansetron, bemesetron and tropisetron on normal and morphine-induced sexual behaviour in female and male rats. There were no effects of these 5-HT_3 receptor antagonists under the conditions tested.

A subsequent study investigated effects of intracerebroventricular administration of 5-HT_3 receptor agonists.[111] In this study, 2-methyl-serotonin had no effects but 1-phenyl-biguanide facilitated sexual activity in males. The effects of the latter compound were related to its direct influence on carrier-mediated dopamine release rather than 5-HT_3 receptor–mediated actions. Thus, there seems to be no evidence for 5-HT_3 receptor–mediated influences on sexual behaviour.

Shepherd and Rodgers[112] reported that ondansetron increased time spent feeding in free-feeding

mice. Administration of tropisetron or bemesetron also increased consumption of amino acid–imbalanced diets in rats,[113] a finding that has been recently confirmed and extended to blockade of aversion to saccharin presented in an imbalanced amino acid diet.[114,115] In contrast, Fletcher and Davies[116] reported that tropisetron increased feeding latency and decreased feeding duration in rats exposed to unfamiliar food but subsequent work indicated that ondansetron had no effects on food intake under a wide variety of feeding conditions.[117] Tropisetron has also been reported to potentiate the anorectic effect of naloxone.[118] Studies with ondansetron have also revealed a potentiation of the anorectic effects of dexamphetamine[119] and a reduction of palatable food consumption in nondeprived rats.[120]

The relevance of these results to appetitive disorders in the clinical context is unknown. The effects of 5-HT_3 receptor antagonists on the gastrointestinal system are well established, particularly in terms of anti-inflammatory responses and gastrointestinal motility, and this has been the major thrust for drug development in this general area.[121]

4. Involvement of 5-HT_3 Receptors in Antidepressant Drug Action

The established role of serotonin in antidepressant action has led to some interest in this potential aspect of 5-HT_3 receptor involvement. There has been some interest in antidepressant effects of 5-HT_3 antagonists, initially based on claims that several antidepressant drugs exhibited nanomolar affinity for [^{3}H]quipazine-labelled 5-HT_3 binding sites. Subsequent analysis using [^{3}H]zacopride and [^{3}H]tropisetron to label 5-HT_3 binding sites did not confirm these claims.[122]

It has recently been reported that the antidepressant drugs clomipramine, fluoxetine and paroxetine interact with both central (NG 108-15 cells) and peripheral 5-HT_3 receptors but do not interact with 5-HT_4 receptors.[123] In addition, in relation to tropisetron, it has been claimed that 5-HT_3 receptors within the prefrontal cortex may play a role in fluoxetine-induced increases in extracellular dopamine within this area, although this was not the case with desipramine.[124]

Electroconvulsive shocks do not alter electrophysiological responses to the 5-HT_3 agonist 2-methyl-serotonin.[125] Fan[126,127] has reported an increase in the rate of 5-HT_3 receptor–mediated current desensitisation and an inhibition of peak serotonin current following application of the antidepressants phenelzine, fluoxetine and imipramine in rat nodose ganglion. These results implicate this receptor in the acute actions of antidepressants and also have implications for the mechanisms of action of these drugs on nociceptive responses.

Complementary results have been reported for mianserin and its 6-aza-analogue mirtazapine (ORG-3770). Both compounds displace 5-HT_3 receptor–related ligand binding and reduce 5-HT_3 receptor–mediated currents in NIE-115 neuroblastoma cells.[128]

Recently, modulation of hippocampal noradrenaline release by the 5-HT_3 receptor agonist 2-methyl-serotonin has been demonstrated in limbic areas of the rat brain, a result with obvious implications for antidepressant potential. Lesioning serotonin neurons with 5,7-dihydroxy-tryptamine did not alter this effect, indicating that the effect is not attributable to a presynaptic serotonin terminal population of receptors.[129]

The novel selective 5-HT_3 receptor agonist SR-57227A tests positively in a variety of laboratory animal screening tests for antidepressant action.[130] This compound is the first of a new class of 5-HT_3 receptor agonists that readily cross the blood-brain barrier,[18] a development that greatly opens up the possibility of exploring effects of 5-HT_3 receptor stimulation in behavioural tests. Also of interest in this area are compounds such as litoxetine, which is a selective serotonin uptake inhibitor with antiemetic properties.[131] Although litoxetine has been withdrawn from development, drugs such as this may prove to be effective antidepressants with a reduced gastrointestinal adverse effect profile, which can be a problem with the

clinical application of this class of antidepressants.[132-134]

Disruption of sleep and related EEG activity is quite prominent in affective illness. Of the few reports available to date only one indicates any interesting effects of 5-HT_3 antagonists on sleep/wakefulness in rats. In this study, ondansetron increased paradoxical (rapid eye movement; REM) sleep. Bemesetron decreased both paradoxical and slow wave sleep and increased wakefulness, but only at a very high dose (10 mg/kg).[135] More recently, tropisetron was found to reduce stage 2 sleep in human volunteers during the entire night and to increase REM sleep during the first third of the night.[136] In this study, total REM remained unaltered.

5. Cognition and the 5-HT_3 Receptor

The ability of 5-HT_3 receptor antagonists to facilitate cholinergic transmission in cortical brain tissue raised the possibility that these compounds might be effective in treating cholinergic dysfunction,[137,138] with the important implication being the possible treatment of cholinergic dysfunction in aging, Alzheimer's disease and other functionally similar disorders.

The early claim for facilitation of cholinergic transmission in brain following treatment with 5-HT_3 receptor antagonists has not been consistently supported. Johnson et al.[139] have reported no significant inhibition or increase in K^+-stimulated acetylcholine release in slices of rat entorhinal cortex following application of a range of 5-HT_3 receptor ligands at a range of concentrations. These authors have suggested that the role of these receptors in modulating release of acetylcholine needs to be re-examined. A study of human cortical cholinergic axon terminals has also demonstrated the 5-HT_3 receptor–mediated inhibition of acetylcholine release.[140]

A more recent study has reported that *stimulation* of 5-HT_3 receptors may induce release of acetylcholine in the dorsal hippocampus of the rat.[141] The latter results are difficult to reconcile with the claims for 5-HT_3 receptor–mediated inhibition of acetylcholine release in the cortex, although Consolo and colleagues[141] have suggested that the actions of 5-HT_3 receptor stimulation may well be regionally selective.

In any event, as both the cortex and hippocampus are important structures in memory processing, the possibility that 5-HT_3 receptor antagonists may be cognitive enhancers is a more complex issue than indicated by the original postulate.[137] Furthermore, it has been suggested that the doses of ondansetron used in published rodent and marmoset studies (10 ng/kg intraperitoneally in rats and mice and 1 and 10 ng/kg subcutaneously in marmosets) are unlikely to be sufficient to increase the release of acetylcholine centrally;[142] this remains an empirical question. Nevertheless, a facilitatory role for 5-HT_3 receptor antagonism in hippocampus is supported by Passani et al.[143] These researchers report an attenuation of serotonin-mediated blockade of long term potentiation in the hippocampus following application of the 5-HT_3 receptor antagonist itasetron (DAU-6215). This compound has been reported to reverse scopolamine (hyoscine)-induced deficits in a spatial learning task in rats[144] and may attenuate scopolamine-induced deficits in passive avoidance learning[145] and in spatial learning.[144] Hodges et al.[146] have recently observed similar effects of the selective 5-HT_3 receptor antagonist WAY-100289 on spatial memory in rats with neurotoxin-induced lesions of the forebrain cholinergic system.

Early results suggested that ondansetron may enhance cognitive performance in rodents and marmosets[49] and may enhance performance of marmosets on an object reversal discrimination task.[138] Ondansetron has also been reported to improve the performance of age-impaired and of atropine-treated rats in a spatial learning task.[147] The effects of scopolamine in a step-through avoidance learning task may also be blocked by tropisetron.[148] In another study of long term potentiation, Stäubli and Xu[149] reported that ondansetron increased the magnitude and duration of this phenomenon. These effects were associated with a dose-dependent increase in hippocampal theta ac-

tivity. In the same study ondansetron also facilitated performance in an odour-matching test and a test of spatial learning.

A failure of ondansetron to reverse scopolamine- or age-related EEG changes in rats has been reported,[150] and Jakala et al.[151] failed to observe an improvement of working memory in a delayed matching to sample task in rats. The group that first reported cognitive-enhancing effects of 5-HT_3 receptor antagonists has recently pointed out that the preclinical literature is now inconsistent in this context.[152] Indeed, these authors reported a failure of ondansetron to attenuate a scopolamine-induced deficit in a Stone maze task and have discussed the apparent task- and dose-related variability of cognitive enhancing effects of these compounds. They point to the heterogeneity of neurochemical substrates underlying regulation of memory processes and to the unusual dose-dependence of 5-HT_3 receptor antagonist effects in this context.

Some evidence has been reported for a enhancement of cognitive functions in human volunteers.[153,154] In a randomised double-blind, double-dummy, 4-way cross-over design healthy male volunteers were tested acutely with the muscarinic antagonist scopolamine and with the 5-HT_3 receptor antagonist alosetron. The verbal memory deficit induced by scopolamine was attenuated by alosetron.[154] In a study of age-associated memory impairment ondansetron was administered to healthy nondemented people over 50 years of age who experienced deterioration of memory performance. Ondansetron was administered twice daily for 12 weeks according to a randomised, double-blind, placebo-controlled design.[153,155] After 12 weeks, the ondansetron-treated group were significantly superior than the placebo group on name-face association acquisition and delayed recall. This effect was dose-dependent, evident at the 250 and 1000μg doses, but the higher dose effects waned by the end of treatment.

These results are somewhat encouraging, but more positive published clinical data are needed. If they are clinically effective compounds in terms of 'cognitive-enhancement' the observation that 5-HT_3 receptors are unaltered in the postmortem analysis of the brains of patients with Alzheimer's disease[156] holds some promise for therapeutic intervention. Nevertheless, in this important area few clinical data have been published to date.

6. Antinociceptive Effects

The ability of the 5-HT_3 agonist 2-methyl-serotonin to mimic, and the antagonists tropisetron and bemesetron to inhibit, peripheral serotonin effects on nociception[157] strongly suggested a role of 5-HT_3 receptors in pain. Nociceptive responses to intravenous serotonin (measured by tail flick and step-down passive avoidance tests) may be mediated by coactivation of 5-HT_2 and 5-HT_3 receptors located on capsaicin-sensitive vagal afferents.[158] In addition, several 5-HT_3 receptor antagonists have been reported to inhibit chemical-induced writhing, an effect that may be attributable to a local rather than a central action.[159] There is considerable evidence for a role for serotonin in the mediation of cardiac pain, and it has been suggested that antagonism of both 5-HT_2 and 5-HT_3 receptors may provide a more effective therapy for treatment of angina and possibly other peripheral serotonin-mediated nociceptive responses.[158]

The presence of a dense band of 5-HT_3 receptors on capsaicin-sensitive primary afferent terminals in the superficial dorsal horn of the spinal cord[160-163] has led to investigation of a nociceptive role for 5-HT_3 receptors at this level.[164] Stimulation of 5-HT_3 receptors by 2-methyl-serotonin blocks scratching and biting induced by substance P and *N*-methyl-D-aspartate (NMDA) applied intrathecally to mice. These antinociceptive effects were blocked by the 5-HT_3 antagonists zacopride and tropisetron, and also by γ-aminobutyric acid (GABA) A and B antagonists, leading to the proposal that 5-HT_3 receptor stimulation in the spinal cord results in a release of GABA which may inhibit nociceptive signal transmission at sites postsynaptic to primary afferent terminals.[164]

It is interesting to note that supersensitivity to 5-HT_3 receptor agonists has not been observed fol-

lowing serotonin denervation by intrathecal application of 5,7-dihydroxy-tryptamine.[165] This observation is in agreement with the observations that these receptors are preferentially located on the terminals of primary afferent fibres and that they are decreased following unilateral rhizotomy.[162] It has been suggested that results such as these with 5-HT_3 receptor–related compounds may herald the development of new nonopioid, nonaddictive analgesics.[164,166]

In addition, 5-HT_3 receptors have now been clearly identified in the gastrointestinal tract in various species,[167] and it seems likely that these sites play a significant role in the regulation or mediation of reflexes governing intestinal movement.[168,169] Several researchers have reported the involvement of these receptor sites in the modulation of visceral hypersensitivity and of stress-induced defecation in rats[170-172] – in contrast with Gué et al.[173] These studies indicate considerable potential for 5-HT_3 receptor antagonists in the treatment of irritable bowel syndrome in humans.

Clinical studies to date have yielded some positive results in this area. Prior and Read[174] reported that ondansetron increased thresholds for perception of sensory effects of rectal distension in patients with irritable bowel syndrome, and similar effects have been observed with granisetron. Ondansetron has, however, been reported to have mixed efficacy in irritable bowel syndrome patients in other studies, and in some cases patients reported increased discomfort.[175-177] In one study, ondansetron did not alter sensitivity to discomfort or measures of colonic function in patients with this disorder.[178] Banner and Sanger[170] have pointed out that the 5-HT_3 receptor antagonists exhibit differential efficacy in the preclinical setting in this context and suggest that, although a correlation between their potencies in preclinical and clinical tests is apparent, this potency does not correlate pharmacologically with the ability of these compounds to antagonise the 5-HT_3 receptor defined *in vitro* or *in vivo* in rats.

It is of considerable interest that clinical benefits have been reported with 5-HT_3 receptor antagonists against the pain of migraine. Whereas bemesetron, granisetron and zatosetron appear to be effective in treating this disorder,[179-182] tropisetron may be only partially effective as an analgesic in this context.[183] In addition, metoclopramide has been broadly used as an analgesic in the clinic;[184-188] however, this compound is not selective for 5-HT_3 receptors.

7. Conclusions

It is clear that the 5-HT_3 receptor is functionally of interest from electrophysiological, molecular and neuropharmacological reports, and as the pharmacological profile of 5-HT_3 receptors in terms of controlling release of noradrenaline, acetylcholine, CCK and dopamine in brain continues to evolve. However, there have been several problems for a realistic evaluation of the behavioural actions of these compounds. One glaring factor is that few groups have published consistent positive findings in areas other than nociception and emesis research. In particular, the bell-shaped dose-response curves which seem to be characteristic of effects of some 5-HT_3 receptor antagonists such as ondansetron and tropisetron in some tests make the choice of doses a critical factor in these experiments. For anxiolytic and antipsychotic studies in particular, there are inconsistencies in the literature which are difficult to understand. It is very important to examine the discrepancies between the preclinical behavioural studies, and to examine the emerging mismatch between some of the behavioural and neuropharmacological results.

One of the most attractive features of 5-HT_3 antagonists is the apparent general lack of adverse effects, which are characteristic of most psychotherapeutic drugs. If positive results with double-blind, placebo-controlled clinical trials are forthcoming then the stimulus provided by the early studies will be really worthwhile. So far, the complexity of the preclinical literature concerning 5-HT_3 receptor pharmacology has not been translated into convincing clinical effects for any disorders other than those associated with the processing of noxious stimuli.

Although we will have to wait and see about the outcome of clinical trials it is apparent that we may have a long wait in relation to CNS disorders: many data may simply never be published because of their negative or inconclusive nature. Although the 5-HT_3 receptor is alive and well in terms of modern biology,[111] it is perhaps a lesson to us all that the tremendous burst of speculative energy based on early preclinical results has been very disappointing in terms of potential therapeutic uses. This in no way detracts from the excellent profile of these drugs for antiemetic and, to some extent, analgesic applications.

The conclusion of the present review is that, while much of the initial preclinical evidence showed spectacular promise for 5-HT_3 receptor antagonists in the treatment of a wide range of disorders, this promise does not seem to have been upheld. This is a position which has not been well received by some researchers in the field and apparently remains contentious. There are possible explanations for the discrepancies which include methodological problems with the initial studies, lack of relevance of some findings with laboratory animals for human conditions, or an inability of the clinical studies to detect subtle effects of 5-HT_3 antagonists. The extent to which studies with non-human species represent 'models' of psychiatric conditions is of pivotal concern in this context. Changes in animal behaviour observed in such studies are interpreted pragmatically and it is clear that such studies do not reach the criteria of an ideal 'model'.

The available data from studies with 5-HT_3 receptor antagonists suggest that results with certain animal models do not correlate well with human clinical responses. This is well illustrated by the odd findings that these compounds test negatively in some well established anxiolytic models (e.g. conflict procedures) but may show some anxiolytic action in the clinic. Similarly, positive results from some laboratory animal tests of antipsychotic drug action contrast markedly against the failure to observe an antipsychotic response in the clinic. This problem is not restricted to 'models' with laboratory animals, for example – the somatic features of anxiety induced by administration of the trazodone metabolite *m*-CPP to human volunteers is blocked by many drugs that have no clinical anxiolytic efficacy.

With this in mind the only pragmatic strategy is to examine drug effects across a wide range of tests to assess their therapeutic potential – in all fairness this has been conducted quite thoroughly in the case of the 5-HT_3 receptor antagonists, with little consistent success. The final possibility is that the 5-HT_3 receptor antagonists do indeed have clinical efficacy but that the clinical studies carried out to date have not been well enough designed to detect these. This issue has been discussed informally by researchers but, to our knowledge, has rarely been entertained in print.

It is necessary to be very careful with this approach. Some studies that we have reviewed[92,105] have demonstrated subtle effects of 5-HT_3 receptor antagonists on human subjective reports. While these phenomena are of interest, they do not address the core symptoms that patients experience, and may not be of any clinical relevance. Indeed, to be fair, we must accept that a number of large pharmaceutical companies have conducted multicentre trials for these compounds for various psychiatric disorders, including schizophrenia. No positive multicentre data have yet been released following these activities, and some companies have apparently dropped these compounds from development for psychotherapeutic potential. Considering the potential benefits to be derived from the development of clinically effective compounds with an apparent lack of undesirable effects, it seems likely that these compounds would be aggressively explored if the clinical profiles were at all positive. Nevertheless, it is unfortunate that negative outcomes of clinical trials are not widely publicised.

The 5-HT_3 receptor is obviously functionally significant in the CNS. It is highly likely that further research into the structure and function of this receptor will yield important new insights into the regulation of mammalian CNS activity which may

have potential for the development of new therapeutic strategies.

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Nervenheilkunde

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Tetrazyklische Antidepressiva:

Pharmakologisch-klinische Aspekte und Neuentwicklungen

Schlüsselwörter
Mianserin, Mirtazapin, Setiptilin, Org 4428, Piperazino-Azepine, tetrazyklische Antidepressiva

Zusammenfassung
Mianserin steht auf dem bundesdeutschen Arzneimittelmarkt seit nunmehr 20 Jahren als einziges »genuines« tetrazyklisches Antidepressivum einer großen und wechselnden Zahl trizyklischer Substanzen gegenüber. Es gehört unter den »neueren« Antidepressiva zu den am besten dokumentierten Substanzen und zeichnet sich, auch in höherer Dosierung, durch sehr gute Verträglichkeit aus. Neben stimmungsaufhellenden, anxiolytischen und schlafanstoßenden Eigenschaften konnte in einer Reihe von Studien die Wirksamkeit von Mianserin gegen weitere Beschwerdebilder, insbesondere Schmerzzustände unterschiedlicher Genese, gezeigt werden. Für 1996 wird die Markteinführung von Mirtazapin in der Bundesrepublik erwartet, eines Antidepressivums, das strukturchemisch wie Mianserin aus einem Ringsystem vom tetrazyklischen Piperazino-Azepintyp besteht, aber ein etwas anderes pharmakologisches Wirkspektrum aufweist. Die antidepressiven Eigenschaften von Mirtazapin sind mittlerweile gut belegt. Wie diese und weitere Entwicklungen (Setiptilin, Org 4428) zeigen, wohnt dem tetrazyklischen Grundgerüst nach Art des Mianserin ein antidepressives Wirkpotential inne, das noch nicht ausgeschöpft ist und neue Möglichkeiten der pharmakopsychiatrischen Therapie eröffnet.

Keywords
Mianserin, mirtazapine, setiptiline, Org 4428, piperazino-azepines, tetracyclic antidepressants

Summary
Mianserin has been on the German market for over 20 years and is the only genuine tetracyclic antidepressant available in the large and changing field of tricyclic substances. Being one of the "newer" antidepessants, it is also one of the best documented compounds, and it has a safe profile of unwanted side effects, even when given in higher dosages. Apart from its effects on mood improvement, reduction of anxiety and sleep enhancement, a number of studies have demonstrated its efficacy against other syndromes, especially pain syndromes of different origin. The introduction of the antidepressant mirtazapine into the German market is expected in 1996. Like mianserin, mirtazapine consists of a tetracyclic structure of the piperazino-azepine type but has a somewhat different pharmacological profile. The antidepressant properties of mirtazapine have been positively acknowledged and demonstrated. In addition, further developments such as setiptiline and Org 4428 show that the beneficial effects of this tetracyclic structure have not yet been exhausted and new possibilities remain to be discovered.

Das Thema des Erlanger nervenärztlichen Fortbildungskongresses 1995 lautete: »Neue Methoden in der Behandlung mit Psychopharmaka«. Hierunter kann folgendes verstanden werden:

1. Änderungen in der Anwendung eines Psychopharmakons im ursprünglichen Indikationsbereich, also zusätzliche Applikationsformen, Höherdosierung oder die Kombination mit anderen psychotropen Substanzen. Beispiele sind die Einführung parenteral applizierbarer Psychopharmaka und der Depot-Neuroleptika. Von Versuchen einer Hochdosisbehandlung mit Neuroleptika Ende der siebziger Jahre ist man bekanntlich wieder abgekommen, aktuell ist dagegen etwa die Hochdosierung pflanzlicher Psychotropika wie des Antidepressivums Hypericin, aber auch verbesserte Therapieerfolge mit dem tetrazyklischen Antidepressivum Mianserin durch höhere Tagesdosen. Die Kombination eines Antidepressivums etwa mit Lithium bewirkt über eine »Augmentation« eine verbesserte Stimmungsaufhellung.
2. Behandlung von Erkrankungen außerhalb des ursprünglichen psychiatrischen Indikationsbereiches mit Psychopharmaka, etwa die Behandlung von Schmerz- und von Entzugssyndromen, aber auch von gastrointestinalen Ulzera oder von juckenden Dermatosen mit trizyklischen Antidepressiva, z. B. Doxepin oder Amitriptylin. Zwangs- und bulimische Störungen sprechen auf selektive Serotonin-Rückaufnahmehemmer (SSRI: Fluoxetin, Fluvoxamin, Paroxetin, Citalopram) an. Lorazepam erwies sich gegen stuporöse Zustände als gut wirksam. Mianserin läßt sich erfolgreich zur Behandlung chronischer Schmerzzustände und unter weiteren Indikationen einsetzen (siehe unten).
3. Behandlungsversuche psychischer Störungen mit Pharmaka aus anderen psychiatrischen oder aus nichtpsychiatrischen Indikationsbereichen. Dabei wurde eine spezielle psychotrope Wirkung entweder zufällig entdeckt (im tierexperimentellen Screening oder bei der klinischen Anwendung) oder aufgrund theoretischer Überlegungen postuliert.

Durch strukturchemische Veränderungen ließ sich oftmals die Eignung einer Substanz für das neue Indikationsgebiet verbessern. Beispiele sind zahlreich, etwa die ersten MAO-Inhibitoren, die – wie Iproniazid – als Tuberkulostatika eingesetzt waren bzw. aus diesen hervorgingen, oder die trizyklischen Antidepressiva (Imipramin), Abkömmlinge der Neuroleptika, letztlich also der Antihistaminika. Auch das Antidepressivum Mianserin ist ein »Nebenprodukt« der Antihistaminikaforschung. Als neuartige potentielle Antidepressiva befinden sich Kalziumantagonisten, ACE-Hemmer, Kortisol-Syntheseinhibitoren und weitere Pharmakagruppen in der Erprobung bzw. Entwicklung (66).

4. Behandlung psychischer Erkrankungen mit neuen Substanzen, die, anders als ältere »dirty drugs« mit ihren vielfältigen Rezeptoraffinitäten, bekannte psychoaktive Wirkprinzipien – etwa auf der Basis der Aminmangelhypothesen – in »reiner« Form verkörpern oder modifiziert aufweisen. Auf dem Antidepressivasektor lassen sich hier die Substanzen der »zweiten Generation« anführen, etwa die SSRI sowie Mianserin und seine Verwandten, insbesondere Mirtazapin als aktuelle Neuentwicklung.

Mianserin: Geschichtliche Entwicklung

Mianserin wurde neben einer Reihe chemisch verwandter Substanzen bei Organon in den Niederlanden als Antiallergikum synthetisiert. Dem Forschungsansatz lag die Hypothese zugrunde, ein Antihistaminikum mit zusätzlichen antiserotonergen Eigenschaften könnte die herkömmlichen Antiallergika an Wirksamkeit übertreffen (80). Tierexperimentelle Testungen ließen – mehr zufällig – verhaltensmodulierende Eigenschaften der Substanz erkennen, die auf eine spezielle zentralnervöse Wirksamkeit von Mianserin hinwiesen; diese konnte auch am Menschen verifiziert werden. Aufgrund computergestützter EEG-Analysen postulierten Itil und Mitarbeiter (Übersicht bei 32) einen antidepressiven Effekt für Mianserin und bestätigten ihn in ersten klinischen Prüfungen.

In Deutschland ist Mianserin seit 1975 als Antidepressivum (Tolvin®) auf dem Arzneimittelmarkt, seit 1991 wird es auch unter dem Handelsnamen Prisma® angeboten.

Chemische Struktur von Mianserin

Mianserin gehört strukturchemisch zu den Piperazino-Azepinen (Abb. 1a). Es ist eine tetrazyklische Verbindung und zeigt keine chemische Verwandtschaft mit den Antidepressiva trizyklischer Grundstruktur. Die Filmtabletten enthalten Mianserin-Hydrochlorid als Razemat, wobei überwiegend das S(+)-Enantiomer für die Blockade der α_2-Autorezeptoren (vgl. unten) und für die verhaltensmodulierenden Eigenschaften in den Depressionsmodellen verantwortlich ist (64).

Pharmakologische Wirkmechanismen von Mianserin

Das pharmakodynamische Profil von Mianserin unterscheidet sich wesentlich von denjenigen anderer Antidepressiva: Der hervorstechende Akuteffekt von Mianserin ist die Blockade kortikaler präsynaptischer α_2-Autorezeptoren, wodurch vermehrt Noradrenalin in den synaptischen Spalt freigesetzt wird (3). Die präsynaptische Wiederaufnahme von Serotonin, Noradrenalin (im therapeutischen Dosisbereich) und von Dopamin wird nicht beeinflußt. Postsynaptisch wirkt Mianserin als mäßiggradiger α_1-Antagonist, kortikale β-Adrenozeptoren werden durch die Substanz nicht beeinflußt (76). Dagegen blockiert Mianserin zentrale postsynaptische Serotonin-(5-Hydroxytryptamin, 5-HT-)Rezeptoren, insbesondere 5-HT_2- und 5-HT_3-, geringer auch 5-HT_1-Rezeptoren. Mianserin wirkt als starker Histamin-H_1- und, auch peripher (Magenschleimhaut!), als Histamin-H_2-Blocker (63). Dagegen werden muskarinische Acetylcholinrezeptoren allenfalls minimal beeinflußt. Anders als die trizyklischen Antidepressiva und ebenso wie die spezifischen Serotonin-Rückaufnahmehemmer zeigt Mianserin einen allenfalls unspezifischen Reserpinantagonismus.

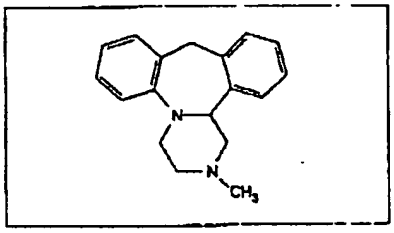

Abb. 1a Chemische Strukturformel von Mianserin (1, 2, 3, 4, 10, 14 b-Hexahydro-2-methyl-dibenzo [c, f] pyrazino-[1, 2a]-azepin)

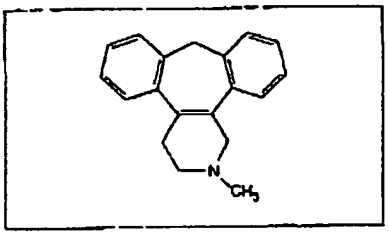

Abb. 1c Chemische Strukturformel von Setiptilin (Teciptilin) (2, 3, 4, 9-Tetrahydro-2-methyl-1H-dibenzo[c,f]cycloheptal[1,2-c]pyridin)

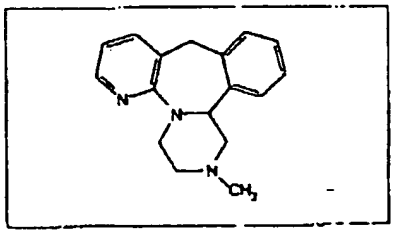

Abb. 1b Chemische Strukturformel von Mirtazapin (1, 2, 3, 4, 10, 14 b-Hexahydro-2-methylpyrazino-[2, 1a] pyrido-[2,3c] [2] benzazepin)

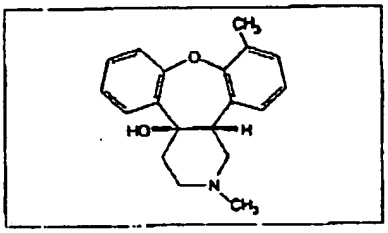

Abb. 1d Chemische Strukturformel von Org 4428 (cis-1, 2, 3, 4, 4a, 13b-Hexahydro-2, 10-dimethyl-dibenz-[2, 3:6, 7]oxepino[4,5-c] pyridin-4a-ol)

Die längerfristige Einwirkung von Mianserin führt tierexperimentell zu einer Abnahme der Wirksamkeit von Agonisten auf das β-adrenozeptorgekoppelte Adenylatzyklasesystem in kortikalen Neuronen (50). Welche Bedeutung dieser Effekt für die klinische Wirksamkeit von Mianserin hat, ist noch unklar. Ähnliches gilt für den Einfluß von Mianserin auf die Aktivierung des Locus coeruleus (Sitz der Noradrenalin-produzierenden Neuronen im Gehirn) durch das Corticotropin releasing hormone (CRH) (17). Eine Abnahme der Dichte postsynaptischer β-Rezeptoren (β-Downregulation) wurde ebenfalls mit der antidepressiven Wirkung der Antidepressiva in Zusammenhang gesehen, doch ist diese Hypothese mittlerweile in Frage gestellt, da unter längerer Mianserin- (auch unter Viloxazin-)Gabe eine β-Downregulation nicht beobachtet werden konnte (5).

Antidepressive Wirksamkeit von Mianserin

Unter den »Antidepressiva der zweiten Generation« gehört Mianserin zu denjenigen Substanzen, deren stimmungsaufhellender Effekt besonders gut belegt ist (56). Gegen Plazebo wurde Mianserin in mindestens acht Effizienzstudien mit zusammen etwa 600 Patienten doppelblind getestet. In fünf dieser Studien fand sich eine signifikante Überlegenheit des Pharmakons. Kontrollierte Untersuchungen gegen trizyklische Referenzpräparate (Amitriptylin/Nortriptylin, Imipramin, Clomipramin, weitere verschiedene Trizyklika) führten zu jeweils gleichwertigen Therapieergebnissen und ließen bezüglich Verträglichkeit und unerwünschter Wirkungen zumeist Vorteile für Mianserin erkennen (56). Gegenüber anderen Antidepressiva der »zweiten Generation« erwies sich Mianserin in Doppelblindprüfungen ebenfalls als jeweils wirkäquivalent bei zumeist gleich guter, teilweise auch besserer Verträglichkeit. Die Vergleichssubstanzen waren Maprotilin, Trazodon (56) und die spezifischen Serotonin-Wiederaufnahmehemmer Fluoxetin, Fluvoxamin, Paroxetin und Citalopram (19). Im Vergleich zu dem reversibel bindenden MAO-A-Hemmer Moclobemid schnitt Mianserin in zwei Doppelblindstudien an älteren Populationen günstig ab, in einer der Studien waren unter Mianserin weniger unerwünschte Wirkungen zu verzeichnen (21, 78). Zwei kontrollierte Vergleiche gegen Diazepam ließen ein gutes anxiolytisches Potential bei depressiv-ängstlichen Patienten erkennen, in der antidepressiven Wirksamkeit war Mianserin dem Benzodiazepin erwartungsgemäß überlegen. Einer Kombination aus Amitriptylin und Chlordiazepoxid erwies sich Mianserin bezüglich der antidepressiven und der anxiolytischen Effizienz als gleichwertig (71).

Im Rahmen kontrollierter Studien wurde Mianserin an ambulanten und stationären Patienten, an Patienten mit schweren Depressionen und an geriatrischen Patienten geprüft. Diagnostisch handelte es sich ganz überwiegend um »major depressive disorders« nach DSM III bzw. DSM-III-R (etwa der endogenen Depression entsprechend), teilweise aber auch um reaktiv bzw. neurotisch depressive Störungen. Eine der wenigen medikamentösen Therapiestudien bei depressiven Kindern und Adoleszenten wurde mit Mianserin in Form einer offenen Pilotstudie durchgeführt (23). Hier ließ sich ebenfalls eine gute Wirksamkeit nachweisen; die mittleren Erhaltungsdosen lagen bei ca. 1 mg/kg Körpergewicht.

Die antidepressive Wirksamkeit von Mianserin steht mittlerweile außer Frage, sie ist derjenigen trizyklischer und neuerer Medikamente zur Behandlung depressiver Störungen gleichwertig (56).

Zur Dosierung von Mianserin

Als Erhaltungsdosis in der Standardbehandlung von Depressionen gilt der Bereich zwischen 60 und 90 mg Mianserin täglich. Dieser Dosisbereich wurde auch in der Mehrzahl der kontrollierten Wirksamkeits- und Vergleichsstudien nicht oder nicht wesentlich überschritten. Neuere Untersuchungen lassen jedoch erkennen, daß höhere Tagesdosen geeignet sind, den Therapieerfolg weiter zu verbessern. In Tabelle 1 sind eine Reihe zumeist kontrollierter Studien aufgelistet, in denen bedarfsweise Tagesdosen bis 150 mg und mehr gegeben wurden. Die in den Arbeiten dargestellten Therapieverläufe zeigen kontinuierliche Besserungen, wobei die Verträglichkeit des Medikamentes durch Höherdosierung nicht beeinträchtigt wird; insbesondere traten keine Blutbildveränderungen auf (vgl. unten). In einigen Studien (z. B. 8) wird über einen früheren Wirkbeginn von Mianserin gegenüber der Vergleichssubstanz berichtet.

Befunde zur Eliminationsgeschwindigkeit von Mianserin beim *älteren* Menschen sind widersprüchlich, aktuelle Untersuchungen fanden jedoch gegenüber jüngeren Altersgruppen keine Besonderheiten (4, 42, 43). Auch beim älteren Patienten kann eine Steigerung der Tagesdosis über 90 mg hinaus den Therapieeffekt günstig beeinflussen (43).

Eine Erhaltungsdosis von Mianserin zwischen 30 und 90 mg pro die ist nach wie vor in den meisten Fällen – zumindest in der ambulanten Verordnung – ausreichend. Sollte sich hierunter allerdings binnen 14 Tagen kein befriedigendes Therapieergebnis einstellen, so erscheint aufgrund der vorliegenden Daten eine schrittweise Steigerung der Tagesdosis, im Bedarfsfalle auf bis zu 180 mg täglich, empfehlenswert. Diesem Umstand trägt die kürzlich erfolgte Einführung einer 60-mg-Tablette für Mianserin (Tolvin®) Rechnung.

Zur Frage der Blutbildveränderungen unter Mianserin

Erste Einzelfälle von Leukozytopenien bzw. Agranulozytosen unter Mianserin wurden Ende der siebziger Jahre aus Großbritannien, später auch aus dem australisch-neuseeländischen Raum berichtet (1, 2, 12, 13, 16, 27, 47, 57, 60). In Neuseeland ergab die Auswertung im Rahmen des Intensive Medicines Monitoring Programme für den Zeitraum von 1983 bis 1988 eine Inzidenz von Agranulozytosen von 1:1822 mianserinbehandelter Patienten (14, 15). In den Fällen, in denen Mianserin als einziges Medikament eingenommen worden war, lag die Inzidenz bei 1:3461 (15). Insgesamt wurden drei Todesfälle erfaßt.

Die Häufung dieser Komplikation scheint allerdings regional begrenzt

Tab. 1 Antidepressive Therapiestudien mit Mianserin, in denen höhere Tagesdosen (>90 mg) erreicht wurden

Autor(en) und Jahr	Studiendesign	vermehrt unerwünschte Arzneimittelwirkungen (UAW) durch Dosiserhöhung > 90 mg ?
McGrath et al. 1985	vs. Placebo (PL) ambulant MIA bis 150 mg	nicht ausdrücklich gesagt, aber auch hohe Dosen gut verträglich
Carman et al. 1991	doppelblind vs. Amitriptylin (AMI) und PL ambulant MIA bis 150 mg nach Bedarf	nein
Wilcox et al. 1994	doppelblind vs. AMI und PL ambulant MIA bis 150 mg nach Bedarf	kein Hinweis
Jaskari et al. 1977	vs. AMI stationär MIA bis 120 mg	keine Aussage: „60-90mg MIA verursachen keine ernsthaften hämatologischen, Leberfunktions- und EKG-Störungen"
Feighner et al. 1983	vs AMI ambulant MIA bis 150 mg (x=105 mg)	keine Aussage, aber insgesamt besser verträglich als AMI
Guy et al. 1983	doppelblind vs. AMI stationär MIA bis 150 mg (x max. 127 mg)	nicht ausdrücklich gesagt, aber weniger Studienabbrüche als unter AMI
Dunbar et al. 1985	vs. Clomipramin ambulant MIA bis 150 mg (teilweise)	keine Zunahme von UAW im Studienverlauf
Perez und Ashford 1990	vs Fluvoxamin ambulant MIA bis 180 mg (teilweise)	nein, initiale Müdigkeit verlieren sich, Studienabbrüche überwiegend initial
de Wilde et al. 1985	vs Citalopram stationär MIA bis 120 mg (10 Pat.)	nein, abnehmende Zahl von Symptomen und UAW im Studienverlauf (Dosissteigerung)
Hodel und Trum 1977	offene Feldstudie ambulant und stationär MIA verzinzelt auf 120 oder 160 mg	nein, vielmehr Verringerung der UAW unter fortlaufender Therapie
Hopman 1986	offene Studie ambulant MIA nach Bedarf bis 120 mg	nein

zu sein: eine umfangreiche britische Vergleichsstudie ergab eine Wahrscheinlichkeit für eine Leukopenie unter Mianserin wie für Amitriptylin zwischen 1:10000 und 1:100000 (34); auch Erhebungen in den alten Bundesländern, u.a. basierend auf Zahlen der Deutschen Arzneimittelkommission, ließen keine statistisch zu sichernde höhere Inzidenz gravierender Blutbildveränderungen unter Mianserin gegenüber anderen Antidepressiva erkennen (52). Aufgrund der neuseeländischen Befunde werden in der Bundesrepublik dennoch wöchentliche Kontrollen des weißen Blutbildes während der ersten Behandlungsmonate empfohlen. In dieser Zeit sollte auch verstärkt auf Zeichen verminderter Immunresistenz (fieberhafte Infekte, Grippe, Tonsillitiden u.a.) geachtet werden. Bei einer Gesamtleukozytenzahl unter 3000 pro mm^3 ist Mianserin abzusetzen und ein Differentialblutbild anzufertigen.

Ältere Patienten scheinen von Blutbildveränderungen unter Antidepressiva, auch unter Mianserin, etwas häufiger betroffen zu sein. Eine Differenz zwischen den Geschlechtern besteht nicht (14). Die Reaktion, von der selten auch andere Blutzellen betroffen sind, fällt bevorzugt in den Zeitraum zwischen vierter und sechster Behandlungswoche. Blutbildveränderungen, ebenfalls zumeist passager, können auch unter der Behandlung mit trizyklischen Antidepressiva auftreten; auch hier sind deshalb regelmäßige Kontrollen – in mehrwöchigen Abständen – angezeigt (5).

Mianserin: Sicherheit bei Überdosierung

Mianserin hat in Überdosis nur geringe toxische Eigenschaften. Es ist daher auch bei potentieller Suizidgefahr ein sehr »sicheres« Medikament (49, 67, 84), im Gegensatz zur überwiegenden Mehrzahl der trizyklischen Substanzen und den älteren MAO-Hemmern (9, 25, 55). In Überdosis verursacht Mianserin Müdigkeit, Anstieg oder Abfall des Blutdrucks, Tachy- oder Bradykardien ohne Arrhythmien (10), bemerkenswerterweise keine epileptischen Anfälle, im Gegensatz zu Intoxikationen mit trizyklischen Antidepressiva oder Maprotilin (38). Einzelfälle von intrakardialen Blockbildungen (28, 31) und rezidivierenden ventrikulären Fibrillationen (30) wurden beschrieben.

Therapeutisch sind bei Intoxikationen mit Mianserin Magenspülung (wenn die Tablettenaufnahme nicht länger als vier Stunden zurückliegt, 49) und ggf. symptomatische Maßnahmen indiziert, ein spezifisches Antidot ist nicht bekannt.

Gibt es weitere Indikationen für Mianserin?

Neben depressiven und depressiv-ängstlichen Verstimmungszuständen sind weitere Indikationen für Mianserin denkbar, die sich aus den Angriffsorten der Substanz an verschiedenen zentralen Rezeptoren ergeben (vgl. oben und 65), teilweise allerdings erst tierexperi-

mentell getestet wurden, z. B. Erbrechen, Opiatentzug oder Aggressivität. Humanstudien liegen vor zur Wirksamkeit, bei primären Angststörungen (6, 58), zur Behandlung schizophrener Negativsyndrome in kombinierter Gabe mit Neuroleptika (51), zu Schlafstörungen (48, 54) und Zwangsstörungen (36, 79). Schon frühzeitig wurde die Substanz auf ihre migräneprophylaktische Wirksamkeit getestet (61). Es folgte eine Reihe kontrollierter Studien zu dieser (53) und anderen Indikationen aus dem Schmerzbereich wie Therapie von Migräne und Spannungskopfschmerz (20), chronischem Spannungskopfschmerz (40), diabetischer (Poly-) Neuropathie (72), chronischem idiopathischem Schmerz als Symptom einer »larvierten« Depression (81) und chronischen Schmerzen unterschiedlicher Genese (59); die drei letztgenannten Studien erbrachten negative Ergebnisse. Manna et al. (44) fanden in einer Vergleichsstudie zu Fluvoxamin eine gute Wirksamkeit von Mianserin gegen mäßiggradige Spannungskopfschmerzen bei Depressionen. Bei relativ niedriger Tagesdosierung (30-60 mg) war Mianserin gegen Spannungskopfschmerzen, nicht jedoch gegen Kreuzschmerzen Plazebo signifikant überlegen (41).

Insgesamt lagen in den genannten Schmerzstudien die Tagesdosen von Mianserin zwischen 30 und 90 mg, also im unteren bis mittleren therapeutisch empfohlenen Bereich. Tanum (77) testete in einer Pilotstudie Mianserin in Tagesdosen zwischen 90 und 120 mg erfolgreich gegen chronische idiopathische Schmerzen des Abdomens, wozu auch Fälle mit irritablem Kolon gehört haben dürften. Unter der gleichen Indikation waren die niedrigeren Dosen in der Studie von Loldrup et al. (41) weniger effizient.

Mianserin erscheint somit gut wirksam in der Migräneprophylaxe, gegen akute Migräne, gegen mäßiggradige Spannungskopfschmerzen und, in höherer Dosierung, möglicherweise auch gegen psychosomatische abdominelle Schmerzen (z. B. Colon irritabile).

Eine aktuelle Neuentwicklung: Mirtazapin (Org 3770)

Eine weitere tetrazyklische Verbindung aus der Reihe der Piperazino-Azepine, für die eine antidepressive Wirksamkeit nachgewiesen wurde, ist Mirtazapin.

Diese Verbindung unterscheidet sich von Mianserin strukturchemisch durch den kondensierten Pyridinring (statt des kondensierten Benzolringes); aus der starken Interaktion des zusätzlichen Stickstoffatoms mit dem benachbarten Stickstoffatom resultiert ein erheblicher Unterschied zwischen beiden Verbindungen in der Verteilung der Elektronendichte und damit auch in den pharmakologischen Eigenschaften (Abb. 1b).

Bei den **pharmakokinetischen** Eigenschaften liegt der Unterschied in der höheren Bioverfügbarkeit von Mirtazapin (Tab. 2).

Pharmakodynamisch ist Mirtazapin wie Mianserin ein α_2-Antagonist, bewirkt also ebenfalls über den präsynaptischen α_2-Autorezeptor eine Anreicherung von Noradrenalin im synaptischen Spalt (Blockade des negativen Feedback in die präsynaptische Zelle) (Abb. 2). Ebenfalls über eine α_2-Blockade kommt es zu einer verstärkten Aktivität serotonerger Neuronen, vermittelt durch α_1-Rezeptoren auf diesen Zellkörpern; im Gegensatz zu Mianserin besitzt Mirtazapin nur eine sehr schwache α_1-adrenolytische Potenz, so daß hier das freigesetzte Noradrenalin mit diesen Rezeptoren nahezu uneingeschränkt interagieren kann. Schließlich wird über eine Blockade auch der α_2-Heterorezeptoren an den serotonergen präsynaptischen Membranen durch Mirtazapin (nicht aber durch Mianserin) die terminale Freisetzung des Serotonins gefördert. Das freigesetzte Serotonin (5-Hydroxytryptamin = 5-HT) wirkt nun agonistisch auf postsynaptische $5\text{-}HT_1$-Rezeptoren, was mit der antidepressiven Wirksamkeit in Zusammenhang gesehen wird, wohingegen die postsynaptischen $5\text{-}HT_2$- und $5\text{-}HT_3$-Rezeptoren durch Mirtazapin blockiert werden: die $5\text{-}HT_2$-Blockade wird mit der schlafverbessernden und anxiolytischen, die $5\text{-}HT_3$-Blockade ebenfalls mit der anxiolytischen Wirkung in Verbindung gebracht (18). Des weiteren verhindert die Blockade der $5\text{-}HT_2$- und der

Tab. 2 Pharmakokinetische Daten von Mianserin und Mirtazapin

Pharmakokinetische Parameter	Mianserin	Mirtazapin
Bioverfügbarkeit:	ca. 20-30 %	50 %
Plasmabindung:	96 %	85 %
Steady state im Plasma erreicht nach:	6 Tagen	3-5 Tagen
Induktion metabolisierender Leberenzyme:	nein	nein
Hauptmetabolisierungswege:	Demethylierung, 8-Hydroxylierung	Demethylierung, 8-Hydroxylierung
aktive Metaboliten:	ja (Desmethylmianserin, 8-Hydroxymianserin)	Desmethylmirtazapin mit ca. 30 % Aktivität und wesentlich geringerer Plasmakonzentration
Plasma-Eliminations-Halbwertszeit:	ca. 30 Stunden	20-40 Stunden
Hauptausscheidungsorgan:	Niere (70 %)	Niere (85 %)

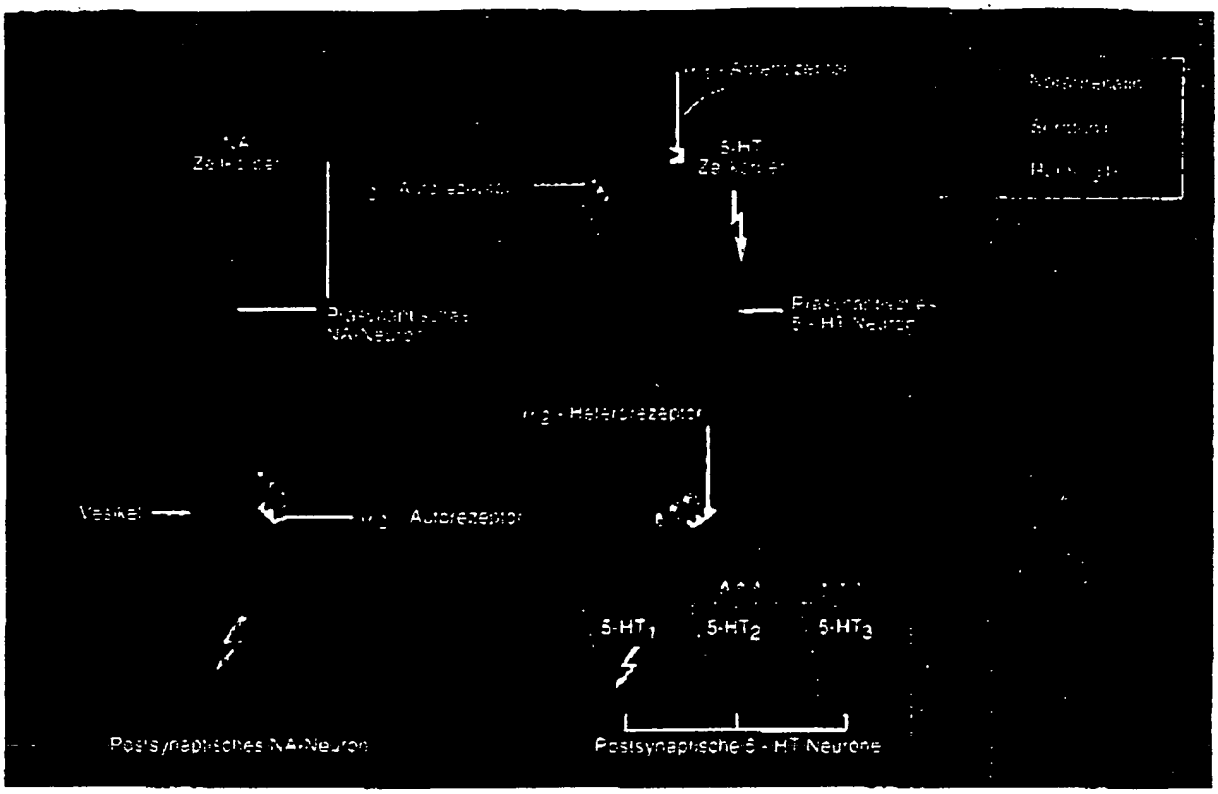

Abb. 2 Schematische Darstellung des pharmakologischen Wirkmechanismus von Mirtazapin, in der Abbildung mit dem Handelsnamen für die BRD (Remergil®) bezeichnet. NA= Noradrenalin, 5-HT= 5-Hydroxytryptamin = Serotonin

5-HT_3-Rezeptoren unerwünschte Begleiteffekte aufgrund unspezifischer Serotoninstimulation, wie sie etwa unter selektiven Serotonin-Wiederaufnahmehemmern (Nausea, Unruhezustände), MAO-Hemmern (Unruhe) und Venlafaxin (Nausea) beobachtet werden.

Der wesentliche Wirkunterschied zwischen den beiden tetrazyklischen Substanzen besteht also darin, daß Mirtazapin zusätzlich zu der noradrenergen Wirkung (wie Mianserin) eine ausgeprägte serotonerge Wirkung aufweist, die sich spezifisch über den 5-HT_1-Rezeptor entfaltet. Die Wirkgruppe, der Mirtazapin – neben evtl. anderen Substanzen – angehört, wird deshalb als »*N*oradrenalin *a*nd *S*pecific *S*erotonin *A*ntidepressant« – NaSSA – bezeichnet (wohl in Anlehnung an den Terminus der »Selective Serotonin Reuptake Inhibitors«, SSRI).

Mirtazapin wurde in kontrollierten Studien auf seine klinische Wirksamkeit gegen depressive Störungen geprüft. Die Tagesdosen in diesen Studien, die (8/95) erst zum Teil publiziert sind, lagen zwischen 15 und 60 mg. Gegenüber Plazebo zeigte sich eine signifikante Überlegenheit (11, 83). Die stimmungsaufhellende Wirkung war derjenigen von Standardantidepressiva wie Amitriptylin (7, 75, 86), Clomipramin (68) und Doxepin (45) ebenbürtig, derjenigen von Trazodon überlegen (82). Die Untersuchungskollektive umfaßten unter anderem Patienten mit schweren Depressionen (Hamilton-Summenscore über 25) und stationäre Patienten (82, 86).

Auch auf Angstsymptome und Schlafstörungen im Rahmen depressiver Erkrankungen hat Mirtazapin einen günstigen Einfluß, wie aus Metaanalysen der plazebo- und amitriptylinkontrollierten Studien hervorgeht (74). Der positive Einfluß auf klinisch relevante Schlafparameter war bereits in tierexperimentellen Studien und an gesunden Probanden (69) gezeigt worden. Primäre Angststörungen sind einer Therapie mit Mirtazapin gut zugänglich (73), doch bedarf diese Indikation – auch wegen ihrer klinisch-praktischen Bedeutung – der Bestätigung durch weitere Studien auf der Basis von ICD-10- oder DSM-Kriterien.

Beim Vergleich der Verträglichkeit von Mirtazapin mit Amitriptylin ergab sich kein Überwiegen unerwünschter Effekte, insbesondere fehlten anticholinerge Begleitwirkungen bei Mirtazapin nahezu vollständig. Im Plazebovergleich traten Sedierung, Appetitsteigerung, Mundtrockenheit und Gewichtszunahme unter Verum häufiger auf, unter Plazebo überwogen Kopfschmerzen und Gewichtsreduktion (74).

Weitere Neuentwicklungen

Seit 1989 ist eine weitere tetrazyklische Verbindung in Japan zugelassen,

Setiptilin oder **Teciptilin** (**Org 8282** oder **MO 8282**, japanischer Handelsname Tecipul, Abb. 1c), das Eigenschaften von Mianserin (potenter Serotonin-, Histamin-H_1- und präsynaptischer α_2-Antagonismus) mit einer Noradrenalin-Wiederaufnahmeinhibition vereinigt. Die Eliminations-Halbwertszeit beträgt ca. 11 Stunden, gebräuchliche Tagesdosen bewegen sich zwischen 6 und 9 mg. Es liegen Wirksamkeitsnachweise zu den Indikationen »Depressionen« (37) und »Negativsymptome der Schizophrenie« (39) vor.

Eine ebenfalls tetrazyklische Substanz in Analogie zur Strukturklasse der Piperazino-Azepine ist derzeit als Antidepressivum in Phase III der klinischen Erprobung (**Org 4428**, Abb. 1d). Es handelt sich, gewissermaßen als Gegenstück zu den SSRI, um einen selektiven Noradrenalin-Wiederaufnahmehemmer (70). Im Sinne der eingangs erwähnten »Verfeinerung« sind daher kaum Interaktionen mit anderen Rezeptoren zu erwarten. Insbesondere zeigt Org 4428 im Gegensatz zu trizyklischen Noradrenalin-Wiederaufnahmehemmern wie Desipramin oder Maprotilin keine anticholinergen Effekte, auch fehlt eine sedierende Begleitwirkung.

Weitere Verbindungen, die Strukturvarianten von Mianserin darstellen, sind als Migränemittel und -prophylaktika bzw. als Antidepressiva mit guten anxiolytischen Eigenschaften in der Erprobung.

Schlußbemerkung

Mianserin hat sich mittlerweile über 20 Jahre lang in der Therapie depressiver Störungen bewährt, und es schien verwunderlich, daß der großen Zahl eingeführter trizyklischer Antidepressiva bislang nur ein »echtes« Tetrazyklikum gegenüberstand. Nunmehr formiert sich, ausgehend von Mianserin, ein neues Arsenal zur Therapie depressiver Störungen. Während die Trizyklika hinsichtlich ihrer therapeutischen und Verträglichkeitseigenschaften eine relativ homogene Gruppe bilden, bringen strukturchemische Variationen des Tetrazyklikums Mianserin eine Reihe neuer Eigenschaften hervor, die therapierelevant sind und gleichzeitig einen Fortschritt im Sinne besserer Verträglichkeit bedeuten. Den theoretischen Hintergrund für den postulierten klinischen Wirkmechanismus bilden weiterhin die Aminmangelhypothesen, die allerdings hier in weitgehend »reiner«, im Falle des Mirtazapins sogar in kombinierter (Noradrenalin *und* Serotonin) Form verwirklicht sind. Das therapeutische Potential, das der tetrazyklischen Grundstruktur des Mianserin innewohnt, ist offenkundig noch nicht ausgeschöpft. Es eröffnen sich hier neue, zweifellos vielversprechende Möglichkeiten für die Pharmakotherapie in der Psychiatrie und vielleicht auch für weitere Gebiete der medikamentösen Behandlung.

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Mechanism of Action of the Antidepressant Mirtazapine

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Objective: We report here on our progress in explaining the properties of the new antidepressant mirtazapine, by its spectrum of affinities for adrenergic and serotonergic receptors.

Method: The techniques used are receptor binding, micro-dialysis and animal behaviour.

Results: Mirtazapine is a powerful antagonist for the presynaptically located α2 receptors and for 5-HT_{2A}, 5-HT_{2B}, 5-HT_{3C} and 5-HT_3 receptors. Similar to noradrenergic terminals the serotonergic terminals undergo inhibitory control by α2 receptor activation. Blockade of these receptors by mirtazapine leads to enhancement of both noradrenergic and serotonergic transmission. This indirect serotonin enhancement leads to indirect activation of those serotonin receptors which are *not* blocked by mirtazapine, such as 5-HT_{1A} receptors. In rats, we studied overt unconditioned symptoms evoked by selective serotonin agonists and by serotonin reuptake inhibitors (SSRI's). Both mirtazapine as well as SSRI's indirectly activate 5-HT_{1A} receptors, whereas 5-HT_{2A}, 5-HT_{2B}, 5-HT_{3C} and 5-HT_3 receptors are blocked by mirtazapine but indirectly activated by SSRI's.

Conclusion: These results suggest that 5-HT_{1A} receptor activation contributes to the antidepressant effect of mirtazapine. Blockade of 5-HT_{2B} and 5-HT_3 receptors can explain the low incidence of typical SSRI related side effects, such as nausea and headache, seen during the clinical use of mirtazapine. Furthermore, blockade rather than activation of 5-HT_{3C} receptors explains that mirtazapine neither has negative impact on sexual functions nor induces appetite inhibition.

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